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**Amphoteric compositions and polymeric forms of alpha hydroxyacids, and their therapeutic use**

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AU9533110

(12) PATENT ABSTRACT (11) Document No. AU-A-33110/95  
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(54) Title  
AMPHOTERIC COMPOSITIONS AND POLYMERIC FORMS OF ALPHA HYDROXYACIDS, AND THEIR THERAPEUTIC USE

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(57) Claim

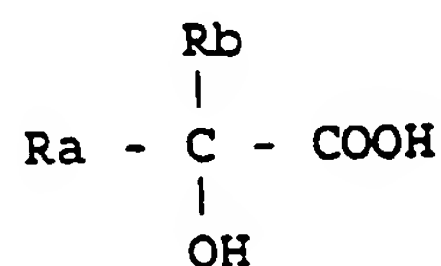
1. A composition comprising a complex formed from the reaction of an amphoteric or pseudoamphoteric agent and at least one compound selected from the group consisting of an alpha hydroxyacid, an alpha ketoacid or a related compound,

said complex being in a topically acceptable vehicle for topical application, said amphoteric or pseudoamphoteric agent being at least one member selected from the group consisting of creatine, aminoaldonic acids, aminouronic acids, lauryl aminopropylglycine, aminoaldaric acids, neuraminic acid, desulfated heparin, deacetylated hyaluronic acid, hyalobiuronic acid, chondrosine, deacetylated chondroitin, creatinine, cocoamphoglycine, cocoamphopropionate, cocoamphopropylsulfonate, phosphatidyl ethanolamine, glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine,

cystine, methionine, asparagine, glutamine, arginine, lysine, 5-hydroxylysine, histidine, phenylalanine, tyrosine, tryptophan, 3-hydroxyproline, 4-hydroxyproline, proline, homocysteine, homocystine, homoserine, ornithine, citrulline, phosphatidyl serine and sphingomyelin,

said amphoteric or pseudoamphoteric agent being present in a concentration effective to form an amphoteric or pseudoamphoteric complex with said alpha hydroxyacid, alpha ketoacid or related compound, wherein said complex reduces the irritation of said alpha hydroxyacid, alpha ketoacid or related compound on the skin;

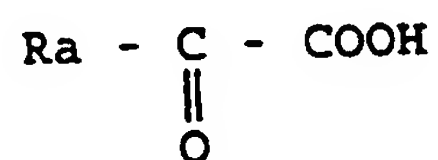
said alpha hydroxyacid being at least one member selected from the group consisting of alkyl alpha hydroxyacid, aralkyl and aryl alpha hydroxyacid, polyhydroxy alpha hydroxyacid and polycarboxylic alpha hydroxyacid having the following chemical structure:



wherein Ra and Rb are H, F, Cl, Br, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain, having 1 to 25 carbon atoms, or cyclic form having 5 or 6 ring members, and in addition Ra and Rb may carry OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms, said alpha hydroxyacid existing as a free acid or

lactone form, or in salt form with an organic base or an inorganic alkali, and a stereoisomers as D, L, and DL forms when Ra and Rb are not identical;

said alpha ketoacid being at least one member selected from a group of compounds represented by the following chemical structure:



wherein Ra is H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain, having 1 to 25 carbon atoms, or cyclic form having 5 or 6 ring members, and in addition Ra may carry F, Cl, Br, I, OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms, said alpha ketoacid existing as a free acid or in a salt form with an organic base or an inorganic alkali; and

said related compound being at least-one member selected from the group consisting of ascorbic acid, quinic acid, isocitric acid, tropic acid, trethocanic acid, 3-chlorolactic acid, cerebronic acid, citramalic acid, agaricic acid, 2-hydroxynervonic acid, aleuritic acid and pantoic acid.

2. The composition of claim 1, wherein said amphoteric or pseudoamphoteric agent is at least one member selected from the group consisting of glycine, alanine, valine, leucine, isoleucine, serine, threonine,



cysteine, cystine, methionine, asparagine, glutamine, arginine, lysine, 5-hydroxylysine, histidine, phenylalanine, tyrosine, tryptophan, 3-hydroxyproline, 4-hydroxyproline, proline, homocysteine, homocystine, homoserine, ornithine, citrulline, creatine, aminoaldonic acids, aminouronic acids, aminoaldaric acids, lauryl aminopropylglycine, neuraminic acid, desulfated heparin, deacetylated hyaluronic acid, hyalobiuronic acid, chondrosine, deacetylated chondroitin, creatinine, cocoamphoglycine, cocoamphopropionate, cocoamphopropylsulfonate, phosphatidyl ethanolamine, phosphatidyl serine and sphingomyelin.

3. The composition of claim 1, wherein said alkyl alpha hydroxyacid is at least one member selected from the group consisting 2-hydroxyethanoic acid (glycolic acid), 2-hydroxypropanoic acid (lactic acid), 2-methyl 2-hydroxypropanoic acid (methyllactic acid), 2-hydroxybutanoic acid, 2-hydroxypentanoic acid, 2-hydroxyhexanoic acid, 2-hydroxyheptanoic acid, 2-hydroxyoctanoic acid, 2-hydroxynonanoic acid, 2-hydroxydecanoic acid, 2-hydroxyundecanoic acid, 2-hydroxydodecanoic acid (alpha hydroxylauric acid), 2-hydroxytetradecanoic acid (alpha hydroxymyristic acid), 2-hydroxyhexadecanoic acid (alpha hydroxypalmitic acid), 2-hydroxyoctadecanoic acid (alpha hydroxystearic acid), 2-hydroxyeicosanoic acid (alpha hydroxy-arachidonic acid).

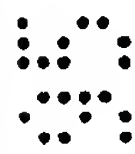
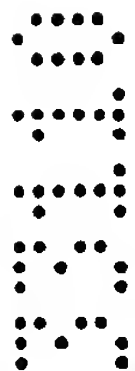
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PATENTS ACT 1990

## COMPLETE SPECIFICATION

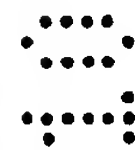
FOR A STANDARD PATENT

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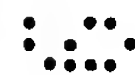
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Invention Title:

"AMPHOTERIC COMPOSITIONS AND POLYMERIC FORMS  
OF ALPHA HYDROXYACIDS, AND THEIR THERAPEUTIC  
USE"

Details of Original Application No. 59139/90 dated 18th July, 1990

The following statement is a full description of this invention, including the best method of performing it known to us:-

AMPHOTERIC COMPOSITION AND POLYMERIC FORMS OF  
ALPHA HYDROXYACIDS, AND THEIR THERAPEUTIC USE

This application is a Divisional of Australian  
Patent Application No. 59139/90, the entire disclosure  
5 of which is incorporated herein by reference.

FIELD OF THE INVENTION

This invention relates generally to therapeutic  
treatment as well as preventive measures for cosmetic  
conditions and dermatologic disorders by topical  
10 administration of amphoteric compositions or polymeric  
forms of alpha hydroxyacids, alpha ketoacids and related  
compounds. We initially discovered that alpha hydroxy  
or ketoacids and their derivatives were effective in the  
topical treatment of disease conditions such as dry  
15 skin, ichthyosis, eczema, palmar and plantar  
hyperkeratoses, dandruff, acne and warts.

We have now discovered that amphoteric  
compositions and polymeric forms of alpha hydroxyacids,  
alpha ketoacids and related compounds on topical  
20 administration are therapeutically effective for various  
cosmetic conditions and dermatologic disorders.

BRIEF DESCRIPTION OF THE PRIOR ART

In our prior U.S. Pat. No. 3,879,537 entitled  
"Treatment of Ichthyosiform Dermatoses" we described and  
25 claimed the use of certain alpha hydroxyacids, alpha  
ketoacids and related compounds for topical treatment of  
fish-scale like ichthyotic conditions in humans. In our  
U.S. Pat. No. 3,920,835 entitled "Treatment of Disturbed  
Keratinization" we described and claimed the use of  
30 these alpha hydroxyacids, alpha ketoacids and their  
derivatives for topical treatment \_\_\_\_\_

of dandruff, acne, and palmar and plantar hyperkeratosis.

5 In our prior U.S. Patent No. 4,105,783 entitled "Treatment of Dry Skin" we described and claimed the use of alpha hydroxyacids, alpha ketoacids and their derivatives for topical treatment of dry skin. In our recent U.S. Patent No. 4,246,261 entitled "Additives Enhancing Topical Corticosteroid Action" we described and claimed that alpha hydroxyacids, alpha ketoacids  
10 and their derivatives, could greatly enhance the therapeutic efficacy of corticosteroids in topical treatment of psoriasis, eczema, seborrheic dermatitis and other inflammatory skin conditions.

15 In our more recent U.S. Patent No. 4,363,815 entitled "Alpha Hydroxyacids, Alpha Ketoacids and Their Use in Treating Skin Conditions" we described and claimed that alpha hydroxyacids and alpha ketoacids related to or originating from amino acids, whether or not found in proteins, were effective in topical  
20 treatment of skin disorders associated with disturbed keratinization or inflammation. These skin disorders include dry skin, ichthyosis, palmar and plantar hyperkeratosis, dandruff, Darier's disease, lichen simplex chronicus, keratoses, acne, psoriasis, eczema,  
25 pruritus, warts and herpes.

In our most recent patent application Serial No. 945,680 filed December 23, 1986 and entitled "Additives Enhancing Topical Actions of Therapeutic Agents" we described and claimed that incorporation of an alpha  
30 hydroxyacid or related compound can substantially enhance therapeutic actions of cosmetic and pharmaceutical agents.

## SUMMARY OF THE INVENTION

There is no doubt that alpha hydroxyacids, alpha ketoacids and related compounds are therapeutically effective for topical treatment of various cosmetic conditions and dermatologic disorders including dry skin, acne, dandruff, keratoses, age spots, wrinkles and disturbed keratinization. However, the compositions containing these acids may irritate human skin on repeated topical applications due to lower pH of the formulations. The irritation may range from a sensation of tingling, itching and burning to clinical signs of redness and peeling. Causes for such irritation may arise from the following:

Upper layers of normal skin have a pH of 4.2 to 5.6, but the compositions containing most alpha hydroxyacids or alpha ketoacids have pH values of less than 3.0. For example, a topical formulation containing 7.6% (1 M) glycolic acid has a pH of 1.9, and a composition containing 9% (1 M) lactic acid has the same pH of 1.9. These compositions of lower pH on repeated topical applications can cause a drastic pH decrease in the stratum corneum of human skin, and provoke disturbances in intercorneocyte bondings resulting in adverse skin reactions, especially to some individuals with sensitive skin.

Moreover, with today's state of the art it is still very difficult to formulate a lotion, cream or ointment emulsion which contains a free acid form of the alpha hydroxyacid, and which is physically stable as a commercial product for cosmetic or pharmaceutical use.

When a formulation containing an alpha hydroxyacid or alpha ketoacid is reacted equimolarly or equinormally with a metallic alkali such as sodium

hydroxide or potassium hydroxide the composition becomes therapeutically ineffective. The reasons for such loss of therapeutic effects are believed to be as follows:

5       The intact skin of humans is a very effective barrier to many natural and synthetic substances. Cosmetic and pharmaceutical agents may be pharmacologically effective by oral or other systematic administration, but many of them are much less or  
10       totally ineffective on topical application to the skin. Topical effectiveness of a pharmaceutical agent depends on two major factors; (a) bioavailability of the active ingredient in the topical preparation and (b) percutaneous absorption, penetration and distribution  
15       of the active ingredient to the target site in the skin. For example, a topical preparation containing 5% salicylic acid is therapeutically effective as a keratolytic, but that containing 5% sodium salicylate is not an effective product. The reason for such  
20       difference is that salicylic acid is in bioavailable form and can penetrate the stratum corneum, but sodium salicylate is not in bioavailable form and cannot penetrate the stratum corneum of the skin.

      In the case of alpha hydroxyacids, a topical  
25       preparation containing 5% glycolic acid is therapeutically effective for dry skin, but that containing 5% sodium glycollate is not effective. The same is true in case of 5% lactic acid versus 5% sodium lactate. The reason for such difference is that both  
30       glycolic acid and lactic acid are in bioavailable forms and can readily penetrate the stratum corneum, but sodium glycollate and sodium lactate are not in bioavailable forms and cannot penetrate the stratum corneum of the skin.



When a formulation containing an alpha hydroxyacid or alpha ketoacid is reacted equimolarly or equinormally with ammonium hydroxide or an organic base of smaller molecule the composition still shows some therapeutic effects for certain cosmetic conditions such as dry skin, but the composition has lost most of its potency for other dermatologic disorders such as wrinkles, keratoses, age spots and skin changes associated with aging.

It has now been discovered that amphoteric compositions containing alpha hydroxyacids, alpha ketoacids or related compounds, and also the compositions containing dimeric or polymeric forms of hydroxyacids overcome the aforementioned shortcomings and retain the therapeutic efficacies for cosmetic conditions and dermatological disorders.

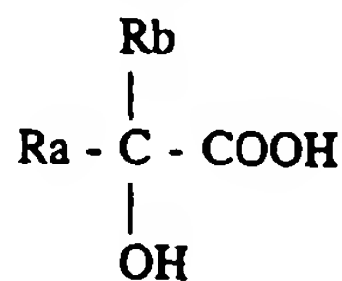
According to a first aspect the present invention consists in a

composition comprising:

- (a) an amphoteric or pseudoamphoteric agent;
- (b) a cosmetic agent or a pharmaceutical agent; and
- (c) an alpha hydroxyacid, an alpha ketoacid or a related compound present in a therapeutically effective amount in a topically acceptable vehicle for topical treatment of cosmetic conditions or dermatologic disorders,

said amphoteric or pseudoamphoteric agent being at least one member selected from the group consisting of dipeptides, creatine, aminoaldonic acids, aminouronic acids, lauryl aminopropylglycine, aminoaldaric acids, neuraminic acid, desulfated heparin, deacetylated hyaluronic acid, hyalobiuronic acid, chondrosine, deacetylated chondroitin, cocoamphoglycine, cocoamphopropionate, cocoamphopropylsulfonate, phosphatidyl ethanolamine, glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, cystine, methionine, asparagine, glutamine, arginine, lysine, creatinine, 5-hydroxylysine, histidine, phenylalanine, tyrosine, tryptophan, 3-hydroxyproline, 4-hydroxyproline, proline, homocysteine, homocystine, homoserine, ornithine, citrulline, phosphatidylserine, and sphingomyelin;

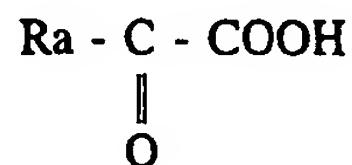
said alpha hydroxyacid being at least one member selected from the group consisting of alkyl alpha hydroxyacid, aralkyl and aryl alpha hydroxyacid, polyhydroxy alpha hydroxyacid and polycarboxylic alpha hydroxyacid having the following chemical structure:





wherein Ra and Rb are H, F, Cl, Br, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric and non-isomeric, straight or branched chain, having 1 to 25 carbon atoms, or cyclic from having 5 or 6 ring members, and in addition Ra and Rb may carry OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms, said alpha hydroxyacid  
5 existing as a free acid or lactone form, or in salt form with an organic base or an inorganic alkali, and as stereoisomers as D, L, and DL forms when Ra and Rb are not identical;

said alpha ketoacid being at least one member selected from a group of compounds represented by the following chemical structure:



10 wherein Ra is H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain, having 1 to 25 carbon atoms, or cyclic form having 5 or 6 ring members, and in addition Ra may carry F, Cl, Br, I, OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms, said alpha ketoacid existing as a free acid or in a salt form with an organic base or an inorganic alkali; and

15 said related compound being at least-one member selected from the group consisting of ascorbic acid, quinic acid, isocitric acid, tropic acid, trethocanic acid, 3-chlorolactic acid, cerebronic acid, citramalic acid, agaricic acid, 2-hydroxynervonic acid, aleuritic acid and pantoic acid.

According to a second aspect the present invention consists  
20 in a composition comprising an acyclic ester of hydroxyacids, present in a therapeutically effective amount in a pharmaceutically acceptable vehicle for topical treatment of cosmetic conditions or dermatologic disorders wherein,

said acyclic ester of hydroxyacids is at least one member having the following structure:



wherein Ra and Rb are H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain, having 1 to 25 carbon atoms, or cyclic form having 5 or 6 ring members, and n is 2 or any number up to 200; Ra and Rb in monomer unit 2 through 200 may be the same or the different groups from that in monomer unit 1; the hydrogen atom in Ra and Rb may be substituted by a halogen atom or a radical of lower alkyl, aralkyl, aryl or alkoxy of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain, having 1 to 9 carbon atoms, or cyclic form having 5 to 6 ring members, and the acyclic esters of hydroxyacids being present as a free acid, ester or in a salt form with an organic base or inorganic alkali in a pharmaceutically acceptable vehicle, and

wherein said acyclic esters of hydroxyacids are formed by the reaction of two or more molecules of hydroxycarboxylic acid, wherein one of the molecules is selected from the group consisting of glycolic acid, lactic acid, mandelic acid, atrolactic acid, citric acid, phenyllactic acid, benzilic acid, tropic acid, trethocanic acid, aleuritic acid, glyceric acid, gluconic acid and gluconolactone, galactonic acid and galactonolactone, glucuronic acid and glucuronolactone, ribonic acid and ribonolactone, galacturonic acid and galacturonolactone, ascorbic acid, gulonic acid and gulonolactone, glucoheptonic acid and glucoheptonolactone, malic acid, citramalic acid, tartronic acid, agaricic acid, isocitric acid, tartaric acid, mucic acid and saccharic acid.

According to a third aspect the present invention consists in a composition comprising a cyclic ester of hydroxyacids, present in a therapeutically effective amount in a pharmaceutically acceptable vehicle for topical treatment of cosmetic conditions and dermatologic disorders wherein,

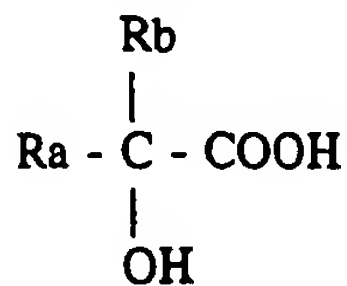
5 said cyclic ester of hydroxyacids is at least one member having the following structure:



wherein Ra and Rb are H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain, having 1 to 25 carbon atoms, or cyclic  
10 form having 5 or 6 ring members, and n is 2 or any number up to 200; Ra and Rb in monomer unit 2 through 200 may be the same or the different groups from that in monomer unit 1; the hydrogen atom in Ra and Rb may be substituted by a halogen atom or a radical of lower alkyl, aralkyl, aryl or alkoxy of saturated or unsaturated, isomeric or non-isomeric,  
15 straight or branched chain, having 1 to 9 carbon atoms, or cyclic form having 5 to 6 ring members, and the acyclic esters of hydroxyacids being present as a free acid, ester or in a salt form with an organic base or inorganic alkali in a pharmaceutically acceptable vehicle.

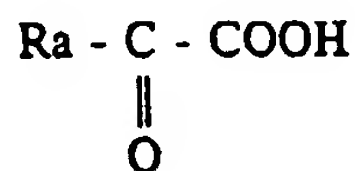
According to a fourth aspect the present invention consists in a method of alleviating aging related skin changes comprising topically applying to a subject in need thereof, a therapeutically effective amount of at least an alpha  
20 hydroxyacid, an alpha ketoacid or a related compound, for a period of time sufficient to alleviate said aging related skin change,

said alpha hydroxyacid being at least one member selected from the group consisting of alkyl alpha hydroxyacid, aralkyl and aryl alpha hydroxyacid, polyhydroxy alpha hydroxyacid and polycarboxylic alpha hydroxyacid having the following chemical structure:



wherein Ra and Rb are H, F, Cl, Br, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-someric, straight or branched chain, having 1 to 25 carbon atoms, or cyclic form having 5 or 6 ring members, and in addition Ra and Rb may carry OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms, said alpha hydroxyacid  
5 existing as a free acid or lactone form, or in salt form with an organic base or an inorganic alkali, and as stereoisomers as D, L, and DL forms when Ra and Rb are not identical:

said alpha ketoacid being at least one member selected from a group of compounds represented by the following chemical structure:



10 wherein Ra is H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain, having 1 to 25 carbon atoms, or cyclic form having 5 or 6 ring members, and in addition Ra may carry F, Cl, Br, I, OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms, said alpha ketoacid existing as a free acid or in a salt form with an organic base or an inorganic alkali; and

15 said related compound being at least-one member selected from the group consisting of ascorbic acid, quinic acid, isocitric acid, tropic acid, trethocanic acid, 3-chlorolactic acid, cerebronic acid, citramalic acid, agaricic acid, 2-hydroxynervonic acid, aleuritic acid and pantoic acid.

Unless the context requires otherwise, throughout the specification, and the claims which follow, the words "comprise", and the like, are to be construed in an inclusive sense, that is as "including, but not limited to".

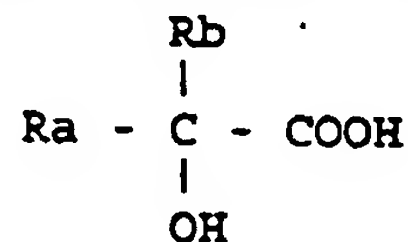
According to a broad aspect the present invention consists in a composition comprising a complex formed from the reaction of an amphoteric or pseudoamphoteric agent and at least one compound selected from the group  
5 consisting of an alpha hydroxyacid, an alpha ketoacid or a related compound,

said complex being in a topically acceptable vehicle for topical application, said amphoteric or pseudoamphoteric agent being at least one member  
10 selected from the group consisting of creatine, aminoaldonic acids, aminouronic acids, lauryl aminopropylglycine, aminoaldaric acids, neuraminic acid, desulfated heparin, deacetylated hyaluronic acid, hyalobiuronic acid, chondrosine, deacetylated  
15 chondroitin, creatinine, cocoamphoglycine, cocoamphopropionate, cocoamphopropylsulfonate, phosphatidyl ethanolamine, glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, cystine, methionine, asparagine, glutamine, arginine,  
20 lysine, 5-hydroxylysine, histidine, phenylalanine, tyrosine, tryptophan, 3-hydroxyproline,

4-hydroxyproline, proline, homocysteine, homocystine, homoserine, ornithine, citrulline, phosphatidyl serine and sphingomyelin,

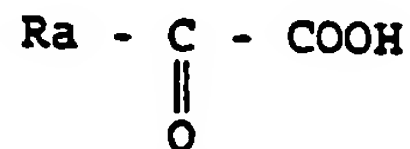
5 said amphoteric or pseudoamphoteric agent being present in a concentration effective to form an amphoteric or pseudoamphoteric complex with said alpha hydroxyacid, alpha ketoacid or related compound, wherein said complex reduces the irritation of said alpha hydroxyacid, alpha ketoacid or related compound on the  
10 skin;

15 said alpha hydroxyacid being at least one member selected from the group consisting of alkyl alpha hydroxyacid, aralkyl and aryl alpha hydroxyacid, polyhydroxy alpha hydroxyacid and polycarboxylic alpha hydroxyacid having the following chemical structure:



20 wherein Ra and Rb are H, F, Cl, Br, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain, having 1 to 25 carbon atoms, or cyclic form having 5 or 6 ring members, and in addition Ra and Rb may carry OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms, said alpha hydroxyacid existing as a free acid or lactone form, or in salt form with an organic base or an inorganic alkali, and a stereoisomers as D, L, and DL  
25 forms when Ra and Rb are not identical;

said alpha ketoacid being at least one member selected from a group of compounds represented by the following chemical structure:



wherein Ra is H, alkyl, aralkyl or aryl group of

5 saturated or unsaturated, isomeric or non-isomeric, straight or branched chain, having 1 to 25 carbon atoms, or cyclic form having 5 or 6 ring members, and in addition Ra may carry F, Cl, Br, I, OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms, said alpha ketoacid existing as a free acid or in a salt form with an organic base or an inorganic alkali; and

10 said related compound being at least-one member selected from the group consisting of ascorbic acid, quinic acid, isocitric acid, tropic acid, trethocanic acid, 3-chlorolactic acid, cerebronic acid, citramalic acid, agaricic acid, 2-hydroxynervonic acid, aleuritic acid and pantoic acid.

15 Such an amphoteric system has a suitable pH, and can release the active form of an alpha hydroxyacid or alpha ketoacid into the skin. The dimeric and polymeric forms of alpha, beta or other hydroxyacids in non-aqueous compositions have a more desired pH than that of the monomeric form of the hydroxyacids. The non-aqueous  
20 compositions can be formulated and induced to release the active form of hydroxyacids after the compositions have been topically applied to the skin. The cosmetic conditions and dermatologic disorders in humans and animals, in which the amphoteric compositions containing  
25 the dimeric or polymeric forms of hydroxyacids may be useful, include dry skin, dandruff, acne, keratoses, psoriasis, eczema, pruritus, age spots, lentigines, melasmas, wrinkles, warts, \_\_\_\_\_



blemished skin, hyperpigmented skin, hyperkeratotic skin, inflammatory dermatoses, skin changes associated with aging and as skin cleansers.

#### DETAILED DESCRIPTION OF THE INVENTION

##### 5 I. Amphoteric and Pseudoamphoteric Compositions

Amphoteric substances by definition should behave either as an acid or a base, and can be an organic or an inorganic compound. The molecule of an organic amphoteric compound should consist of at least one  
10 basic and one acidic group. The basic groups include, for example, amino, imino and guanido groups. The acidic groups include, for example, carboxylic, phosphoric and sulfonic groups. Some examples of organic amphoteric compounds are amino acids, peptides,  
15 polypeptides, proteins, creatine, aminoaldonic acids, aminouronic acids, lauryl aminopropylglycine, aminoaldaric acids, neuraminic acid, desulfated heparin, deacetylated hyaluronic acid, hyalobiuronic acid, chondrosine and deacetylated chondroitin.

20 Inorganic amphoteric compounds are certain metallic oxides such as aluminum oxide and zinc oxide.

Pseudoamphoteric compounds are either structurally related to true amphoteric compounds or capable of inducing the same function when they are incorporated  
25 into the compositions containing alpha hydroxyacids or ketoacids. Some examples of pseudoamphoteric compounds are creatinine, stearamidoethyl diethylamine, stearamidoethyl diethanolamine, stearamidopropyl dimethylamine, quaternary ammonium hydroxide and  
30 quaternium hydroxide.

The amphoteric composition of the instant invention contains in combination an alpha hydroxyacid or alpha ketoacid and an amphoteric or pseudoamphoteric compound. There are two advantages of utilizing an

amphoteric or the like compound in the therapeutic composition containing an alpha hydroxy or ketoacid. These are (a) the overall pH of the composition is raised, so that the composition becomes less or non-irritating to the skin and (b) some alpha hydroxy or ketoacid molecules react with the amphoteric compound to form a quadruple ionic complex which acts as buffering system to control the release of alpha hydroxy or ketoacid into the skin, therefore, eliminating the skin irritation and still retaining the therapeutic efficacies.

The following are some examples. 2-Hydroxyethanoic acid (glycolic acid) 1 M aqueous solution has pH 1.9. The pHs of compositions change to 3.0 and 3.2 when arginine 0.5 M and creatinine 0.5 M respectively are incorporated into the formulations. 2-Hydroxypropanoic acid (lactic acid) 1 M aqueous solution has pH 1.9. The pHs of compositions change to 3.1 and 6.9 when arginine 0.5 M and 1.0 M respectively are incorporated into the formulations. 2-Methyl 2-hydroxypropanoic acid (methyllactic acid) 1 M aqueous solution has pH 1.9. The pHs of compositions change to 3.3, 3.4 and 3.2 when 0.5 M each of arginine, creatinine and 4-aminobutanoic acid respectively are incorporated into the formulations. 2-Hydroxybutane-1,4-dioic acid (malic acid) 1 M aqueous solution has pH 1.8, but the pH of the composition changes to 3.0 when creatinine 0.5 M is incorporated into the formulation.

Ideally, an amphoteric compound should contain both anionic and cationic groups or functional groups capable of behaving both as an acid and a base. Although inorganic amphoteric compounds such as aluminum oxide, aluminum hydroxide and zinc oxide may be utilized, organic amphoteric compounds have been

found to be more efficient in formulating therapeutic compositions of the instant invention.

Organic amphoteric and pseudoamphoteric compounds may be classified into three groups, namely (a) amino acid type, (b) imidazoline and lecithin amphoterics and (c) pseudoamphoterics and miscellaneous amphoterics.

(a) Amino acid type amphoterics. Amphoteric compounds of amino acid type include all the amino acids, dipeptides, polypeptides, proteins and the like which contain at least one of the basic groups such as amino, imino, guanido, imidazolino and imidazolyl, and one of the acidic groups such as carboxylic, sulfonic, sulfinic and sulfate.

Glycine is a simple amphoteric compound which contains only one amino group and one carboxylic group. Lysine contains two amino groups and one carboxylic group. Aspartic acid contains one amino group and two carboxylic groups. Arginine contains one amino group, one guanido group and one carboxylic group. Histidine contains one amino group, one imidazolyl group and one carboxylic group. Taurine contains one amino group and one sulfonic group. Cysteine sulfinic acid contains one amino group, one carboxylic group and one sulfinic group. The amino group of an amphoteric compound may also be substituted, such as in betaine which is a glycine N,N,N-trimethyl inner salt.

Glycylglycine is a simple dipeptide which contains one free amino group and one free carboxylic group. Glycylhistidine is also a dipeptide which contains one free amino group, one imidazolyl group and one free carboxylic group.

The representative amphoteric compounds of amino acid type may be listed as follows: Glycine, alanine, valine, leucine, isoleucine, serine, threonine,

cysteine, cystine, methionine, aspartic acid, asparagine, glutamic acid, glutamine, arginine, lysine, 5-hydroxylysine, histidine, phenylalanine, tyrosine, tryptophan, 3-hydroxyproline, 4-hydroxyproline and proline.

5

The related amino acids include homocysteine, homocystine, homoserine, ornithine, citrulline, creatine, 3-aminopropanoic acid, theanine, 2-aminobutanoic acid, 4-aminobutanoic acid, 2-amino-2-methylpropanoic acid, 2-methyl-3-aminopropanoic acid, 2,6-diaminopimelic acid, 2-amino-3-phenylbutanoic acid, phenylglycine, canavanine, canaline, 4-hydroxyarginine, 4-hydroxyornithine, homoarginine, 4-hydroxyhomoarginine,  $\beta$ -lysine, 2,4-diaminobutanoic acid, 2,3-diaminopropanoic acid, 2-methylserine, 3-phenylserine and betaine.

10

15

Sulfur-containing amino acids include taurine, cysteinesulfinic acid, methionine sulfoxide and methionine sulfone.

20

The halogen-containing amino acids include 3,5-diiodotyrosine, thyroxine and moniodotyrosine. The imino type acids include pipecolic acid, 4-aminopipecolic acid and 4-methylproline.

25

The dipeptides include for example, glycylglycine, carnosine, anserine, ophidine, homocarnosine,  $\beta$ -alanyllysine,  $\beta$ -alanylarginine. The tripeptides include for example, glutathione, ophthalmic acid and norophthalmic acid. Short-chain polypeptides of animal, plant and bacterial origin containing up to 100 amino acid residues include bradykinin and glucagon. The preferred proteins include for example protamines, histones and other lysine and arginine rich proteins.

30

(b) Imidazoline and lecithin amphoteric. The amphoteric compounds of imidazoline derived type are

commercially synthesized from 2-substituted-2-imidazolines obtained by reacting a fatty acid with an aminoethylethanolamine. These amphoterics include cocoamphoglycine, cocoamphopropionate, and cocoamphopropylsulfonate. The amphoteric compounds of lecithin and related type include for example, phosphatidyl ethanolamine, phosphatidyl serine and sphingomyelin.

(c) Pseudoamphoterics and miscellaneous amphoterics. Many pseudoamphoteric compounds are chemically related or derived from true amphoterics. For example, creatinine is derived from creatine. Other pseudoamphoteric compounds may include fatty amide amines such as stearamidoethyl diethylamine, stearamidoethyl diethanolamine and stearamidopropyl dimethylamine. Other pseudoamphoteric related compounds include quaternary ammonium hydroxide and quaternium hydroxide.

In accordance with the present invention, the alpha hydroxyacid, the alpha ketoacids and the related compounds which are incorporated into amphoteric or pseudoamphoteric compositions for cosmetic conditions and dermatologic disorders may be classified into three groups.

The first group is organic carboxylic acids in which one hydroxyl group is attached to the alpha carbon of the acids. The generic structure of such alpha hydroxyacids may be represented as follows:



where Ra and Rb are H, F, Cl, Br, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and in addition Ra and Rb may carry OH, CHO, COOH and alkoxy group having

1 to 9 carbon atoms. The alpha hydroxyacids may be present as a free acid or lactone form, or in a salt form with an organic base or an inorganic alkali. The alpha hydroxyacids may exist as stereoisomers as D, L, and DL forms when Ra and Rb are not identical.

Typical alkyl, aralkyl and aryl groups for Ra and Rb include methyl, ethyl, propyl, isopropyl, butyl, pentyl, octyl, lauryl, stearyl, benzyl and phenyl, etc. The alpha hydroxyacids of the first group may be divided into (1) alkyl alpha hydroxyacids, (2) aralkyl and aryl alpha hydroxyacids, (3) polyhydroxy alpha hydroxyacids, and (4) polycarboxylic alpha hydroxyacids. The following are representative alpha hydroxyacids in each subgroup.

(1) Alkyl Alpha Hydroxyacids

1. 2-Hydroxyethanoic acid (Glycolic acid, hydroxyacetic acid)



2. 2-Hydroxypropanoic acid (Lactic acid)



3. 2-Methyl 2-hydroxypropanoic acid (Methylactic acid)



4. 2-Hydroxybutanoic acid



5. 2-Hydroxypentanoic acid



6. 2-Hydroxyhexanoic acid



7. 2-Hydroxyheptanoic acid



8. 2-Hydroxyoctanoic acid





9. 2-Hydroxynonanoic acid  
(C<sub>9</sub>H<sub>17</sub>) (H) C (OH) COOH
10. 2-Hydroxydecanoic acid  
(C<sub>10</sub>H<sub>18</sub>) (H) C (OH) COOH
- 5 11. 2-Hydroxyundecanoic acid  
(C<sub>11</sub>H<sub>19</sub>) (H) C (OH) COOH
12. 2-Hydroxydodecanoic acid (Alpha hydroxylauric acid)  
(C<sub>12</sub>H<sub>21</sub>) (H) C (OH) COOH
- 10 13. 2-Hydroxytetradecanoic acid (Alpha hydroxymyristic acid)  
(C<sub>14</sub>H<sub>25</sub>) (H) C (OH) COOH
14. 2-Hydroxyhexadecanoic acid (Alpha hydroxypalmitic acid)  
(C<sub>16</sub>H<sub>29</sub>) (H) C (OH) COOH
- 15 15. 2-Hydroxyoctadecanoic acid (Alpha hydroxystearic acid)  
(C<sub>18</sub>H<sub>33</sub>) (H) C (OH) COOH
16. 2-Hydroxyeicosanoic acid (Alpha hydroxyarachidonic acid)  
(C<sub>20</sub>H<sub>37</sub>) (H) C (OH) COOH
- 20
- (2) Aralkyl And Aryl Alpha Hydroxyacids
1. 2-Phenyl 2-hydroxyethanoic acid (Mandelic acid)  
(C<sub>6</sub>H<sub>5</sub>) (H) C (OH) COOH
- 25 2. 2,2-Diphenyl 2-hydroxyethanoic acid (Benzilic acid)  
(C<sub>6</sub>H<sub>5</sub>) (C<sub>6</sub>H<sub>5</sub>) C (OH) COOH
3. 3-Phenyl 2-hydroxypropanoic acid (Phenyllactic acid)  
(C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>) (H) C (OH) COOH
- 30 4. 2-Phenyl 2-methyl 2-hydroxyethanoic acid (Atrolactic acid)  
(C<sub>6</sub>H<sub>5</sub>) (CH<sub>3</sub>) C (OH) COOH



5. 2-(4'-Hydroxyphenyl) 2-hydroxyethanoic acid  
(4-Hydroxymandelic acid)  
(HO-C<sub>6</sub>H<sub>4</sub>) (H) C (OH) COOH
- 5 6. 2-(4'-Chlorophenyl) 2-hydroxyethanoic acid  
(4-Chloromandelic acid)  
(Cl-C<sub>6</sub>H<sub>4</sub>) (H) C (OH) COOH
7. 2-(3'-Hydroxy-4'-methoxyphenyl) 2-hydroxyethanoic acid  
(3-Hydroxy-4-methoxymandelic acid)  
10 (HO-,CH<sub>3</sub>O-C<sub>6</sub>H<sub>3</sub>) (H) C (OH) COOH
8. 2-(4'-Hydroxy-3'-methoxyphenyl) 2-hydroxyethanoic acid  
(4-Hydroxy-3-methoxymandelic acid)  
(HO-,CH<sub>3</sub>O-C<sub>6</sub>H<sub>3</sub>) (H) C (OH) COOH
- 15 9. 3-(2'-Hydroxyphenyl) 2-hydroxypropanoic acid  
[3-(2'-Hydroxyphenyl) lactic acid]  
HO-C<sub>6</sub>H<sub>4</sub>-CH<sub>2</sub>(H) C (OH) COOH
10. 3-(4'-Hydroxyphenyl) 2-hydroxypropanoic acid  
[3-(4'-Hydroxyphenyl) lactic acid]  
20 HO-C<sub>6</sub>H<sub>4</sub>-CH<sub>2</sub> (H) C (OH) COOH
11. 2-(3',4'-Dihydroxyphenyl) 2-hydroxyethanoic acid  
(3,4-Dihydroxymandelic acid)  
HO-,HO-C<sub>6</sub>H<sub>3</sub> (H) C (OH) COOH
- (3) Polyhydroxy Alpha Hydroxyacids
- 25 1. 2,3-Dihydroxypropanoic acid (Glyceric acid)  
(HOCH<sub>2</sub>) (H) C (OH) COOH
2. 2,3,4-Trihydroxybutanoic acid (Isomers; erythronic acid, threonic acid)  
HOCH<sub>2</sub> (HO)CH<sub>2</sub> (H) C (OH) COOH
- 30 3. 2,3,4,5-Tetrahydroxypentanoic acid (Isomers; ribonic acid, arabinoic acid, xylonic acid, lyxonic acid)  
HOCH<sub>2</sub> (HO)CH<sub>2</sub> (HO)CH<sub>2</sub> (H) C (OH) COOH

4. 2,3,4,5,6-Pentahydroxyhexanoic acid (Isomers; allonic acid, altronic acid, gluconic acid, mannoic acid, gulonic acid, idonic acid, galactonic acid, talonic acid)
- 5  $\text{HOCH}_2 (\text{HO})\text{CH}_2 (\text{HO})\text{CH}_2 (\text{HO})\text{CH}_2 (\text{H}) \text{C} (\text{OH}) \text{COOH}$
5. 2,3,4,5,6,7-Hexahydroxyheptanoic acid (Isomers; glucoheptonic acid, galactoheptonic acid etc.)
- $\text{HOCH}_2 (\text{HO})\text{CH}_2 (\text{HO})\text{CH}_2 (\text{HO})\text{CH}_2 (\text{HO})\text{CH}_2 (\text{H}) \text{C} (\text{OH}) \text{COOH}$
- 10 (4) Polycarboxylic Alpha Hydroxyacids
1. 2-Hydroxypropane-1,3-dioic acid (Tartronic acid)
- $\text{HOOC} (\text{H}) \text{C} (\text{OH}) \text{COOH}$
2. 2-Hydroxybutane-1,4-dioic acid (Malic acid)
- $\text{HOOC} \text{CH}_2 (\text{H}) \text{C} (\text{OH}) \text{COOH}$
- 15 3. 2,3-Dihydroxybutane-1,4-dioic acid (Tartaric acid)
- $\text{HOOC} (\text{HO})\text{CH} (\text{H}) \text{C} (\text{OH}) \text{COOH}$
4. 2-Hydroxy-2-carboxypentane-1,5-dioic acid (Citric acid)
- $\text{HOOC} \text{CH}_2 \text{C} (\text{OH}) (\text{COOH}) \text{CH}_2 \text{COOH}$
- 20 5. 2,3,4,5-Tetrahydroxyhexane-1,6-dioic acid (Isomers; saccharic acid, mucic acid etc.)
- $\text{HOOC} (\text{CHOH})_4 \text{COOH}$
- (5) Lactone Forms
- The typical lactone forms are gluconolactone, galactonolactone, glucuronolactone, galacturonolactone, gulonolactone, ribonolactone, saccharic acid lactone, pantoyllactone, glucoheptonolactone, mannonolactone, and galactoheptonolactone.
- 25
- The second group of compounds which may be incorporated into amphoteric or pseudoamphoteric compositions for cosmetic conditions and dermatologic disorders, is organic carboxylic acids in which the alpha carbon of the acids is in keto form. The generic
- 30

structure of such alpha ketoacids may be represented as follows:



5 wherein Ra and Rb are H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and in addition Ra may carry F, Cl, Br, I, OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms. The alpha ketoacids may be present as a  
10 free acid or an ester form, or in a salt form with an organic base or an inorganic alkali. The typical alkyl, aralkyl and aryl groups for Ra and Rb include methyl, ethyl, propyl, isopropyl, butyl, pentyl, octyl, lauryl, stearyl, benzyl and phenyl, etc.

15 In contrast to alpha hydroxyacids the ester form of alpha ketoacids has been found to be therapeutically effective for cosmetic and dermatologic conditions and disorders. For example, while ethyl lactate has a minimal effect, ethyl pyruvate is therapeutically very  
20 effective. Although the real mechanism for such difference is not known, we have speculated that the ester form of an alpha ketoacid is chemically and/or biochemically very reactive, and a free acid form of the alpha ketoacid is released in the skin after the  
25 topical application.

The representative alpha ketoacids and their esters which may be useful in amphoteric or pseudoamphoteric compositions for cosmetic conditions and dermatologic disorders are listed below:

- 30 1. 2-Ketoethanoic acid (Glyoxylic acid)  
(H) CO COOH  
2. Methyl 2-ketoethanoate  
(H) CO COOCH<sub>3</sub>

3. 2-Ketopropanoic acid (Pyruvic acid)  
 $\text{CH}_3 \text{ CO COOH}$
4. Methyl 2-ketopropanoate (Methyl pyruvate)  
 $\text{CH}_3 \text{ CO COOCH}_3$
- 5 5. Ethyl 2-ketopropanoate (Ethyl pyruvate)  
 $\text{CH}_3 \text{ CO COOC}_2\text{H}_5$
6. Propyl 2-ketopropanoate (Propyl pyruvate)  
 $\text{CH}_3 \text{ CO COOC}_3\text{H}_7$
7. 2-Phenyl-2-ketoethanoic acid (Benzoylformic acid)  
10  $\text{C}_6\text{H}_5 \text{ CO COOH}$
8. Methyl 2-phenyl-2-ketoethanoate (Methyl benzoylformate)  
 $\text{C}_6\text{H}_5 \text{ CO COOCH}_3$
9. Ethyl 2-phenyl-2-ketoethanoate (Ethyl benzoylformate)  
15  $\text{C}_6\text{H}_5 \text{ CO COOC}_2\text{H}_5$
10. 3-Phenyl-2-ketopropanoic acid (Phenylpyruvic acid)  
 $\text{C}_6\text{H}_5\text{CH}_2 \text{ CO COOH}$
11. Methyl 3-phenyl-2-ketopropanoate (Methyl phenylpyruvate)  
20  $\text{C}_6\text{H}_5\text{CH}_2 \text{ CO COOCH}_3$
12. Ethyl 3-phenyl-2-ketopropanoate (Ethyl phenylpyruvate)  
 $\text{C}_6\text{H}_5\text{CH}_2 \text{ CO COOC}_2\text{H}_5$
13. 2-Ketobutanoic acid  
25  $\text{C}_2\text{H}_5 \text{ CO COOH}$
14. 2-Ketopentanoic acid  
 $\text{C}_3\text{H}_7 \text{ CO COOH}$
15. 2-Ketohexanoic acid  
30  $\text{C}_4\text{H}_9 \text{ CO COOH}$
16. 2-Ketoheptanoic acid  
 $\text{C}_5\text{H}_{11} \text{ CO COOH}$
17. 2-Ketooctanoic acid  
 $\text{C}_6\text{H}_{13} \text{ CO COOH}$

## 18. 2-Ketododecanoic acid



## 19. Methyl 2-ketooctanoate



5 The third group of compounds which may be incorporated into amphoteric or pseudoamphoteric compositions for cosmetic and dermatologic conditions and disorders, is chemically related to alpha hydroxyacids or alpha ketoacids, and can be represented  
10 by their names instead of the above two generic structures. The third group of compounds include ascorbic acid, quinic acid, isocitric acid, tropic acid, trethocanic acid, 3-chlorolactic acid, cerebronic acid, citramalic acid, agaricic acid, 2-  
15 hydroxynervonic acid, aleuritic acid and pantoic acid.

## II. Dimeric and Polymeric Forms of Hydroxyacids

When two or more molecules of hydroxycarboxylic acids either identical or non-identical compounds are reacted chemically to each other, dimeric or polymeric  
20 compounds will be formed. Such dimeric and polymeric compounds may be classified into three groups, namely (a) acyclic ester, (b) cyclic ester and (c) miscellaneous dimer and polymer.

(a) Acyclic ester. The acyclic ester of a  
25 hydroxycarboxylic acid may be a dimer or a polymer. The dimer is formed from two molecules of a hydroxycarboxylic acid by reacting the carboxyl group of one molecule with the hydroxy group of a second molecule. For example, glycolyl glycollate is formed  
30 from two molecules of glycolic acid by eliminating one mole of water molecule. Likewise, lactyl lactate is formed from two molecules of lactic acid. When two molecules of different hydroxycarboxylic acids are intermolecularly reacted, a different dimer is formed.

For example, glycolyl lactate is formed by reacting the carboxyl group of lactic acid with the hydroxy group of glycolic acid. The polymer is formed in a similar manner but from more than two molecules of a hydroxycarboxylic acid. For example, glycoly glycoly glycollate is formed from three molecules of glycolic acid. Copolymer is formed from two or more than two different kinds of hydroxycarboxylic acids. For example, glycolyl lactyl glycollate is formed from two molecules of glycolic acid and one molecule of lactic acid.

The acyclic ester of dimeric and polymeric hydroxycarboxylic acids may be shown by the following chemical structure:



wherein Ra, Rb=H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and n=1 or any numerical number, with a preferred number of up to 200. Ra and Rb in monomer unit 2, 3, 4 and so on may be the same or the different groups from that in monomer unit 1. For example, Ra, Rb=H in monomer unit 1, and Ra=CH<sub>3</sub>, Rb=H in monomer unit 2 when n=2 is a dimer called lactyl glycollate, because the first monomer is glycollate unit and the second monomer is lactic acid unit. The hydrogen atom in Ra and Rb may be substituted by a halogen atom or a radical such as a lower alkyl, aralkyl, aryl or alkoxy of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 9 carbon atoms. The dimer and polymer of a hydroxycarboxylic acid may be present as a free acid, ester or salt form with organic base or inorganic alkali.

The typical alkyl, aralkyl and aryl groups for Ra and Rb include methyl, ethyl, propyl, isopropyl, butyl, benzyl and phenyl. Representative acyclic esters of hydroxycarboxylic acids which may be useful for cosmetic conditions and dermatologic disorders are listed below:

1. Glycolyl glycollate (Glycolic acid glycollate)  
Ra,Rb=H in units 1 & 2, n=2
2. Lactyl lactate (Lactic acid lactate)  
Ra=CH<sub>3</sub>, Rb=H in units 1&2, n=2
3. Mandelyl mandellate  
Ra=C<sub>6</sub>H<sub>5</sub>, Rb=H in units 1 & 2, n=2
4. Atrolactyl atrolactate  
Ra=C<sub>6</sub>H<sub>5</sub>, Rb=CH<sub>3</sub> in units 1 & 2, n=2
5. Phenyllactyl phenyllactate  
Ra=C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>, Rb=H, in units 1 & 2, n=2
6. Benzilyl benzillate  
Ra,Rb=C<sub>6</sub>H<sub>5</sub> in units 1 & 2, n=2
7. Glycolyl lactate  
Ra=CH<sub>3</sub> in unit 1, Ra=H in unit 2, Rb=H in units 1 & 2, n=2
8. Lactyl glycollate  
Ra=H in unit 1, Ra=CH<sub>3</sub> in unit 2, Rb=H in units 1 & 2, n=2
9. Glycolyl glycolyl glycollate  
Ra,Rb=H in units 1, 2 & 3, n=3
10. Lactyl lactyl lactate  
Ra=CH<sub>3</sub>, Rb=H in units 1, 2 & 3, n=3
11. Lactyl glycolyl lactate  
Ra=CH<sub>3</sub> in units 1 & 3, Ra=H in unit 2, Rb=H in units 1, 2 & 3, n=3
12. Glycolyl glycolyl glycolyl glycollate  
Ra,Rb=H in units 1, 2, 3 & 4, n=4



## 13. Lactyl lactyl lactyl lactate

Ra=CH<sub>3</sub>, Rb=H in units 1, 2, 3 & 4, n=4

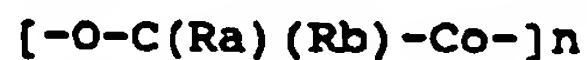
## 14. Glycolyl lactyl glycolyl lactyl glycollate

Ra=H in units 1, 3 & 5, Ra=CH<sub>3</sub> in units 2 & 4,

5 Rb=H in units 1, 2, 3, 4 &amp; 5, n=5

## 15. Polyglycolic acid and polylactic acid

(b) Cyclic ester. The cyclic ester of a hydroxycarboxylic acid may also be a dimer or polymer, the most common type however, is a dimer form. The cyclic dimer may be formed from an identical monomer or different monomers. For example, glycolide is formed from two molecules of glycolic acid by removing two molecules of water, and lactide is formed from two molecules of lactic acid in the same manner. The cyclic ester of dimeric and polymeric hydroxycarboxylic acids may be shown by the following chemical structure:



wherein Ra, Rb=H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and n=1 or any numerical number, however with a preferred number of 2. Ra and Rb in units 1, 2, 3 and so on may be the same or the different groups. For example, in glycolide Ra and Rb are H in both units 1 & 2, but in lactoglycolide Ra is H in unit 1, CH<sub>3</sub> in unit 2 and Rb is H in both units 1 & 2. The hydrogen atom in Ra and Rb may be substituted by a halogen atom or a radical such as a lower alkyl, aralkyl, aryl or alkoxy of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 9 carbon atoms.

The typical alkyl, aralkyl and aryl groups for Ra and Rb include methyl, ethyl, propyl, isopropyl, butyl, benzyl and phenyl. Representative cyclic esters of

hydroxycarboxylic acids which may be useful for cosmetic conditions and dermatologic disorders are listed below:

1. Glycolide  
5       $R_a, R_b = H, n=2$
2. Lactide  
     $R_a = CH_3, R_b = H$  in units 1 & 2,  $n=2$
3. Mandelide  
     $R_a = C_6H_5, R_b = H$  in units 1 & 2,  $n=2$
- 10    4. Atrolactide  
     $R_a = C_6H_5, R_b = CH_3$  in units 1 & 2,  $n=2$
5. Phenyllactide  
     $R_a = C_6H_5, R_b = H$  in units 1 & 2,  $n=2$
6. Benzilide  
15     $R_a, R_b = C_6H_5$  in units 1 & 2,  $n=2$
7. Methyllactide  
     $R_a, R_b = CH_3$  in units 1 & 2,  $n=2$
8. Lactoglycolide  
     $R_a = H$  in unit 1,  $R_a = CH_3$  in unit 2  
20     $R_b = H$  in units 1 & 2,  $n=2$
9. Glycolactide  
     $R_a = CH_3$  in unit 1,  $R_a = H$  in unit 2  
     $R_b = H$  in units 1 & 2,  $n=2$
- 25    (c) Miscellaneous dimer and polymer. This group includes all the dimeric and polymeric forms of hydroxycarboxylic acids, which can not be represented by any one of the above two generic structures, such as those formed from tropic acid, trethocanic acid and aleuritic acid. When a hydroxycarboxylic acid has more  
30    than one hydroxy or carboxy group in the molecule a complex polymer may be formed. Such complex polymer may consist of acyclic as well as cyclic structures.

The following hydroxycarboxylic acids have more than one hydroxy groups: glyceric acid, gluconic acid

and gluconolactone, galactonic acid and galactonolactone, glucuronic acid and glucuronolactone, ribonic acid and ribonolactone, galacturonic acid and galacturonolactone, ascorbic acid, gulonic acid and gulonolactone, glucoheptonic acid and glucoheptonolactone. These polyhydroxycarboxylic acids can form complex polymers with themselves or with other simple monohydroxymonocarboxylic acids.

The following hydroxycarboxylic acids have more than one carboxyl groups: malic acid, citric acid, citramalic acid, tartronic acid, agaricic acid and isocitric acid. These monohydroxypolycarboxylic acids can also form complex polymers with themselves or with other simple hydroxycarboxylic acids.

The following hydroxycarboxylic acids have more than one hydroxy and more than one carboxyl groups: tartaric acid, mucic acid and saccharic acid. These polyhydroxypolycarboxylic acids can form even more complex polymers with themselves or with other hydroxycarboxylic acids.

### III. Combination Compositions

Any cosmetic and pharmaceutical agents may be incorporated into amphoteric or pseudoamphoteric compositions, or into compositions containing dimeric or polymeric forms of hydroxyacids with or without amphoteric or pseudoamphoteric systems to enhance therapeutic effects of those cosmetic and pharmaceutical agents to improve cosmetic conditions or to alleviate the symptoms of dermatologic disorder. Cosmetic and pharmaceutical agents include those that improve or eradicate age spots, keratoses and wrinkles; analgesics; anesthetics; antiacne agents; antibacterials; antiyeast agents; antifungal agents; antiviral agents; antidandruff agents; antidermatitis

agents; antipruritic agents; antiemetics; antimotion  
 sickness agents; antiinflammatory agents;  
 antihyperkeratolytic agents; antidryskin agents;  
 antiperspirants; antipsoriatic agents; antiseborrheic  
 5 agents; hair conditioners and hair treatment agents;  
 antiaging and antiwrinkle agents; antiasthmatic agents  
 and bronchodilators; sunscreen agents; antihistamine  
 agents; skin lightening agents; depigmenting agents;  
 vitamins; corticosteroids; tanning agents; hormones;  
 10 retinoids; topical cardiovascular agents and other  
 dermatologicals.

Some examples of cosmetic and pharmaceutical  
 agents are clotrimazole, ketoconazole, miconazole,  
 griseofulvin, hydroxyzine, diphenhydramine, pramoxine,  
 15 lidocaine, procaine, mepivacaine, monobenzone,  
 erythromycin, tetracycline, clindamycin, meclocycline,  
 hydroquinone, minocycline, naproxen, ibuprofen,  
 theophylline, cromolyn, albuterol, retinoic acid, 13-  
 cis retinoic acid, hydrocortisone, hydrocortisone 21-  
 20 acetate, hydrocortisone 17-valerate, hydrocortisone 17-  
 butyrate, betamethasone valerate, betamethasone  
 dipropionate, triamcinolone acetonide, fluocinonide,  
 clobetasol propionate, benzoyl peroxide, crotamiton,  
 propranolol, promethazine, vitamin A palmitate and  
 25 vitamin E acetate.

#### IV. Specific Compositions For Skin Disorders

We have discovered that topical formulations or  
 compositions containing specific alpha hydroxyacids or  
 alpha ketoacids, or related compounds are  
 30 therapeutically very effective for certain skin  
 disorders without utilizing any amphoteric or  
 pseudoamphoteric systems. The alpha hydroxyacids and  
 the related compounds include 2-hydroxyethanoic acid,  
 2-hydroxypropanoic acid, 2-methyl 2-hydroxypropanoic

acid, 2-phenyl 2-hydroxyethanoic acid, 2,2-diphenyl 2-hydroxyethanoic acid, 2-phenyl 2-methyl 2-hydroxyethanoic acid and 2-phenyl 3-hydroxypropanoic acid. The alpha ketoacids and their esters include 2-  
 5 ketopropanoic acid, methyl 2-ketopropanoate and ethyl 2-ketopropanoate. The mentioned skin disorders include warts, keratoses, age spots, acne, nail infections, wrinkles and aging related skin changes.

10 In general, the concentration of the alpha hydroxyacid, the alpha ketoacid or the related compound used in the composition is a full strength to an intermediate strength, therefore the dispensing and the application require special handling and procedures.

15 If the alpha hydroxyacid, or the alpha ketoacid or the related compound at full strength (usually 95-100%) is a liquid form at room temperature such as 2-hydroxypropanoic acid, 2-ketopropanoic acid, methyl 2-ketopropanoate and ethyl 2-ketopropanoate, the liquid compound with or without a gelling agent is directly  
 20 dispensed as 0.5 to 1 ml aliquots in small vials.

If the alpha hydroxyacid, or the alpha ketoacid or the related compound at full strength is a solid form at room temperature such as 2-hydroxyethanoic acid, 2-methyl 2-hydroxypropanoic acid, 2-phenyl 2-hydroxyethanoic acid, 2,2-diphenyl 2-hydroxyethanoic acid and 2-phenyl 3-hydroxypropanoic acid, the solid  
 25 compound is first dissolved in a minimal amount of vehicle or vehicle system such as water, or ethanol and propylene glycol with or without a gelling agent. For  
 30 example, 2-hydroxyethanoic acid 70 g is dissolved in water 30 g, and the 70% strength solution thus obtained is dispensed as 0.5 to 1 ml aliquots in small vials. If a gelling agent is used, 0.5 to 3% of for example, hydroxyethyl cellulose, methyl cellulose, hydroxypropyl

cellulose or carbomer may be incorporated into the above solution.

5 To prepare an intermediate strength (usually 20-50%), the alpha hydroxyacid, alpha ketoacid or related compound either a liquid or solid form at room temperature is first dissolved in a vehicle or vehicle system such as water, acetone, ethanol, propylene glycol and butane 1,3-diol. For example, 2-hydroxyethanoic acid or 2-ketopropanoic acid 30 g is  
10 dissolved in ethanol 56 g and propylene glycol 14 g, and the 30% strength solution thus obtained is dispensed as 7 to 14 ml aliquots in dropper bottles.

15 For topical treatment of warts, keratoses, age spots, acne, nail infections, wrinkles or aging related skin changes, patients are advised to apply a small drop of the medication with a toothpick or a fine-caliber, commonly available artist's camel hair brush to affected lesions only and not surrounding skin. Prescribed applications have been 1 to 6 times daily  
20 for keratoses and ordinary warts of the hands, fingers, palms, and soles. For age spots, acne, nail infections, wrinkles and aging related skin changes topical applications have been 1 to 2 times daily.

25 Very often, frequency and duration of applications have been modified according to clinical responses and reactions of the lesions and the patient or responsible family member is instructed accordingly. For example, some clinical manifestations other than pain have been used as a signal to interrupt application. These  
30 manifestations include distinct blanching of the lesions or distinct peripheral erythema.

Alternatively, an office procedure may be adapted when a full strength of 2-ketopropanoic acid or 70% 2-



hydroxyethanoic acid is used for topical treatment of age spots, keratoses, acne, warts or facial wrinkles.

We have found that the above mentioned alpha hydroxyacids, alpha ketoacids and related compounds are therapeutically effective for topical treatments of warts, keratoses, age spots, acne, nail infections, wrinkles and aging related skin changes.

Preparation of the Therapeutic Compositions

Amphoteric and pseudoamphoteric compositions of the instant invention may be formulated as solution, gel, lotion, cream, ointment, shampoo, spray, stick, powder or other cosmetic and pharmaceutical preparations.

To prepare an amphoteric or pseudoamphoteric composition in solution form at least one of the aforementioned amphoteric or pseudoamphoteric compounds and in combination at least one of the hydroxyacids or the related compounds are dissolved in a solution which may consist of ethanol, water, propylene glycol, acetone or other pharmaceutically acceptable vehicle. The concentration of the amphoteric or pseudoamphoteric compound may range from 0.01 to 10 M, the preferred concentration ranges from 0.1 to 3 M. The concentration of hydroxyacids or the related compounds may range from 0.02 to 12 M, the preferred concentration ranges from 0.2 to 5 M.

In the preparation of an amphoteric or pseudoamphoteric composition in lotion, cream or ointment form, at least one of the amphoteric or pseudoamphoteric compounds and one of the hydroxyacids or the related compounds are initially dissolved in a solvent such as water, ethanol and/or propylene glycol. The solution thus prepared is then mixed in a conventional manner with commonly available cream or



ointment base such as hydrophilic ointment or petrolatum. The concentrations of amphoteric or pseudoamphoteric compounds and hydroxyacids used in the compositions are the same as described above.

5 Amphoteric and pseudoamphoteric compositions of the instant invention may also be formulated in a gel form. A typical gel composition of the instant invention utilizes at least one of the amphoteric or  
10 pseudoamphoteric compounds and one of the hydroxyacids or the related compounds are dissolved in a mixture of ethanol, water and propylene glycol in a volume ratio of 40:40:20, respectively. A gelling agent such as  
15 methyl cellulose, ethyl cellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carbomer or ammoniated glycyrrhizinate is then added to the mixture with agitation. The preferred concentration of the gelling agent may range from 0.1 to 4 percent by weight of the total composition.

20 Since dimeric and polymeric forms of hydroxyacids are less stable in the presence of water or the like vehicle, cosmetic and pharmaceutical compositions should be prepared as anhydrous formulations. Typical vehicles suitable for such formulations include mineral  
25 oil, petrolatum, isopropyl myristate, isopropyl palmitate, diisopropyl adipate, octyl palmitate, acetone, squalene, squalane, silicone oils, vegetable oils and the like. Therapeutic compositions containing dimeric or polymeric forms of hydroxyacids do not  
30 require any incorporation of an amphoteric or pseudoamphoteric compound. The concentration of the dimeric or polymeric form of a hydroxyacid used in the composition may range from 0.1 to 100%, the preferred concentration ranges from 1 to 40%. Therapeutic

compositions may be formulated as anhydrous solution, lotion, ointment, spray, powder or the like.

To prepare a combination composition in a pharmaceutically acceptable vehicle, a cosmetic or pharmaceutical agent is incorporated into any one of the above composition by dissolving or mixing the agent into the formulation.

The following are illustrative examples of formulations and compositions according to this invention. Although the examples utilize only selected compounds and formulations, it should be understood that the following examples are illustrative and not limited. Therefore, any of the aforementioned amphoteric or pseudoamphoteric compounds, hydroxyacids, dimeric or polymeric forms of hydroxyacids may be substituted according to the teachings of this invention in the following examples.

EXAMPLE 1

An amphoteric composition containing 1 M 2-hydroxyethanoic acid and 0.5 M L-arginine in solution form for dandruff or dry skin may be formulated as follows.

2-Hydroxyethanoic acid (glycolic acid) 7.6 g is dissolved in water 60 ml and propylene glycol 20 ml. L-Arginine 8.7 g is added to the solution with stirring until all the crystals are dissolved. Ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.0. An amphoteric composition formulated from 1 M 2-hydroxyethanoic acid and 1 M L-arginine has pH 6.3. The solution has pH 1.9 if no amphoteric compound is incorporated.

EXAMPLE 2

An amphoteric composition containing 1 M 2-hydroxyethanoic acid and 0.5 M L-lysine in a cream form for dry skin and other dermatologic and cosmetic conditions may be formulated as follows.

2-Hydroxyethanoic acid 7.6 g and L-lysine 7.3 g are dissolved in 30 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.3.

EXAMPLE 3

An amphoteric composition containing 1 M 2-hydroxyethanoic acid and 0.5 M 4-aminobutanoic acid in lotion form for cosmetic and dermatologic conditions may be formulated as follows.

2-Hydroxyethanoic acid 7.6 g and 4-aminobutanoic acid 5.2 g are dissolved in water 30 ml, and the solution is mixed with 50 g of an oil-in-water emulsion. The lotion thus obtained is made up to 100 ml in volume with more oil-in-water emulsion. The amphoteric composition thus formulated has pH 3.1.

EXAMPLE 4

A pseudoamphoteric composition containing 1 M 2-hydroxyethanoic acid and 0.5 M creatinine in solution form for cosmetic conditions and dermatologic disorders may be formulated as follows.

2-Hydroxyethanoic acid 7.6 g is dissolved in water 70 ml and propylene glycol 10 ml. Creatinine 5.7 g is added to the solution with stirring until all the crystals are dissolved. More water is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has pH 3.2. The composition has pH 4.0 when 1 M instead of 0.5 M creatinine is incorporated into the formulation.

#### EXAMPLE 5

10 An amphoteric composition containing 1 M 2-hydroxyethanoic acid and 0.5 M L-histidine in a cream form for dermatologic and cosmetic conditions may be formulated as follows.

15 2-Hydroxyethanoic acid 7.6 g and L-histidine 7.8 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.2.

#### EXAMPLE 6

20 An amphoteric composition containing 0.5 M 2-hydroxyethanoic acid and 0.5 M dipeptide of  $\beta$ -Ala-L-His for cosmetic and dermatologic conditions may be formulated as follows.

25 2-Hydroxyethanoic acid 3.8 g and L-carnosine ( $\beta$ -alanyl-L-histidine) 11.3 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals

have been dissolved sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 4.5.

EXAMPLE 7

5        An amphoteric composition containing 0.5 M 2-hydroxyethanoic acid and 0.5 M cycloleucine for cosmetic and dermatologic conditions may be formulated as follows.

10        2-Hydroxyethanoic acid 3.8 g and 1-aminocyclopentane-1-carboxylic acid (cycloleucine) 6.5 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The amphoteric  
15        composition thus formulated has pH 3.2.

EXAMPLE 8

20        A pseudoamphoteric composition containing 0.5 M 2-hydroxyethanoic acid and 0.25 M 1,12-diaminododecane for cosmetic and dermatologic conditions may be formulated as follows.

25        2-Hydroxyethanoic acid 3.8 g and 1.12-diaminododecane 5 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The

pseudoamphoteric composition thus formulated has pH 4.2.

#### EXAMPLE 9

5 An amphoteric composition containing 0.5 M 2-hydroxyethanoic acid and 5% protamine for cosmetic and dermatologic conditions may be formulated as follows.

10 2-Hydroxyethanoic acid 3.8 g and protamine 5 g, isolated and purified from salmon sperm are dissolved in water 25 ml. The solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.2.

#### EXAMPLE 10

15 An amphoteric composition containing 1 M 2-hydroxypropanoic acid and 0.5 M L-arginine in solution form for dandruff or dry skin may be formulated as follows.

20 2-Hydroxypropanoic acid (DL-lactic acid) USP grade 9.0 g is dissolved in water 60 ml and propylene glycol 20 ml. L-Arginine 8.7 g is added to the solution with stirring until all the crystals are dissolved. Ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.1. An amphoteric composition formulated from 1 M 2-hydroxypropanoic acid and 1 M L-arginine has pH 6.9.

25

The solution has pH 1.9 if no amphoteric compound is incorporated.

EXAMPLE 11

5 An amphoteric composition containing 1 M 2-hydroxypropanoic acid and 0.5 M L-lysine in a cream form for dry skin and other dermatologic and cosmetic conditions may be formulated as follows.

10 2-Hydroxypropanoic acid 9.0 g and L-lysine 7.3 g are dissolved in 30 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.6. An amphoteric composition formulated from 1 M 2-hydroxypropanoic acid and 1 M L-lysine has pH 8.4

EXAMPLE 12

15 An amphoteric composition containing 1 M 2-hydroxypropanoic acid and 0.5 M 4-aminobutanoic acid in lotion form for cosmetic and dermatologic conditions may be formulated as follows.

20 2-Hydroxypropanoic acid 9.0 g and 4-aminobutanoic acid 5.2 g are dissolved in water 30 ml, and the solution is mixed with 50 g of an oil-in-water emulsion. The lotion thus obtained is made up to 100 ml in volume with more oil-in-water emulsion. The  
25 amphoteric composition thus formulated has pH 3.0



pseudoamphoteric composition thus formulated has pH 4.2.

EXAMPLE 9

5 An amphoteric composition containing 0.5 M 2-hydroxyethanoic acid and 5% protamine for cosmetic and dermatologic conditions may be formulated as follows.

10 2-Hydroxyethanoic acid 3.8 g and protamine 5 g, isolated and purified from salmon sperm are dissolved in water 25 ml. The solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.2.

EXAMPLE 10

15 An amphoteric composition containing 1 M 2-hydroxypropanoic acid and 0.5 M L-arginine in solution form for dandruff or dry skin may be formulated as follows.

20 2-Hydroxypropanoic acid (DL-lactic acid) USP grade 9.0 g is dissolved in water 60 ml and propylene glycol 20 ml. L-Arginine 8.7 g is added to the solution with stirring until all the crystals are dissolved. Ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.1. An amphoteric composition formulated from 1 M 2-hydroxypropanoic acid and 1 M L-arginine has pH 6.9.

25

The solution has pH 1.9 if no amphoteric compound is incorporated.

EXAMPLE 11

5 An amphoteric composition containing 1 M 2-hydroxypropanoic acid and 0.5 M L-lysine in a cream form for dry skin and other dermatologic and cosmetic conditions may be formulated as follows.

10 2-Hydroxypropanoic acid 9.0 g and L-lysine 7.3 g are dissolved in 30 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.6. An amphoteric composition formulated from 1 M 2-hydroxypropanoic acid and 1 M L-lysine has pH 8.4

15

EXAMPLE 12

An amphoteric composition containing 1 M 2-hydroxypropanoic acid and 0.5 M 4-aminobutanoic acid in lotion form for cosmetic and dermatologic conditions may be formulated as follows.

20

2-Hydroxypropanoic acid 9.0 g and 4-aminobutanoic acid 5.2 g are dissolved in water 30 ml, and the solution is mixed with 50 g of an oil-in-water emulsion. The lotion thus obtained is made up to 100 ml in volume with more oil-in-water emulsion. The amphoteric composition thus formulated has pH 3.0

25

EXAMPLE 13

A pseudoamphoteric composition containing 1 M 2-hydroxypropanoic acid and 0.5 M creatinine in solution form for cosmetic conditions and dermatologic disorders may be formulated as follows.

2-Hydroxypropanoic acid 9.0 g is dissolved in water 70 ml and propylene glycol 10 ml. Creatinine 5.7 g is added to the solution with stirring until all the crystals are dissolved. More water is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has pH 3.3. The composition has pH 4.4 when 1 M instead of 0.5 M creatinine is incorporated into the formulation.

EXAMPLE 14

An amphoteric composition containing 1 M 2-hydroxypropanoic acid and 1 M L-histidine in a cream form for dermatologic and cosmetic conditions may be formulated as follows.

2-Hydroxypropanoic acid 9.0 g and L-histidine 15.5 g are dissolved in 35 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated as pH 4.9.

EXAMPLE 15

An amphoteric composition containing 1 M 2-hydroxypropanoic acid and 1 M dipeptide of Gly-Gly for

cosmetic and dermatologic conditions may be formulated as follows.

2-Hydroxypropanoic acid 9.0 g and glycylglycine 13.2 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.0.

EXAMPLE 16

10 An amphoteric composition containing 1 M 2-methyl-2-hydroxypropanoic acid and 0.5 M L-arginine in solution form for dandruff or dry skin may be formulated as follows.

15 2-Methyl-2-hydroxypropanoic acid (methyllactic acid) 10.4 g is dissolved in water 60 ml and propylene glycol 20 ml. L-Arginine 8.7 g is added to the solution with stirring until all the crystals are dissolved. Ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.3. An amphoteric composition formulated from 1 M 2-methyl-2-hydroxypropanoic acid and 1 M L-arginine has pH 6.5. The solution has pH 1.9 if no amphoteric compound is incorporated.

EXAMPLE 17

25 An amphoteric composition containing 1 M 2-methyl-2-hydroxypropanoic acid and 0.5 M 4-aminobutanoic acid

in a cream form for dry skin and other dermatologic and cosmetic conditions may be formulated as follows.

2-Methyl-2-hydroxypropanoic acid 10.4 g and 4-aminobutanoic acid 5.2 g are dissolved in 30 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.2.

#### EXAMPLE 18

10 An amphoteric composition containing 1 M 2-methyl-2-hydroxypropanoic acid and 1 M dipeptide of Gly-Gly in lotion form for cosmetic and dermatologic conditions may be formulated as follows.

15 2-Methyl-2-hydroxypropanoic acid 10.4 g and glycylglycine 13.2 g are dissolved in water 30 ml, and the solution is mixed with 50 g of an oil-in-water emulsion. The lotion thus obtained is made up to 100 ml in volume with more oil-in-water emulsion. The amphoteric composition thus formulated has pH 3.0.

20

#### EXAMPLE 19

A pseudoamphoteric composition containing 1 M 2-methyl-2-hydroxypropanoic acid and 0.5 M creatinine in solution form for cosmetic conditions and dermatologic disorders may be formulated as follows.

25 2-Methyl-2-hydroxypropanoic acid 10.4 g is dissolved in water 70 ml and propylene glycol 10 ml.

Creatinine 5.7 g is added to the solution with stirring until all the crystals are dissolved. More water is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has pH 3.4. The composition has pH 4.4 when 1 M instead of 0.5 M creatinine is incorporated into the formulation.

#### EXAMPLE 20

An amphoteric composition containing 0.5 M 2-phenyl-2-hydroxyethanoic acid and 0.5 M L-histidine in a cream form for dermatologic and cosmetic conditions may be formulated as follows.

2-Phenyl 2-hydroxyethanoic acid (mandelic acid) 7.6 g and L-histidine 7.8 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 5.0. The composition has pH 2.2 if no amphoteric compound is incorporated.

#### EXAMPLE 21

An amphoteric composition containing 0.5 M 2-phenyl-2-hydroxyethanoic acid and 0.5 M L-lysine for cosmetic and dermatologic conditions may be formulated as follows.

2-Phenyl 2-hydroxyethanoic acid 7.6 g and L-lysine 7.3 g are dissolved in 25 ml of water. The solution thus obtained is mixed with an oil-in-water emulsion to

make a total volume of 100 ml. The amphoteric composition thus formulated for pH 4.6.

EXAMPLE 22

5 A pseudoamphoteric composition containing 0.5 M 2-phenyl 2-hydroxyethanoic acid and 0.5 M creatinine for cosmetic and dermatologic conditions may be formulated as follows.

10 2-Phenyl 2-hydroxyethanoic acid 7.6 g and creatinine 5.7 g are dissolved in 30 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 4.6.

EXAMPLE 23

15 An amphoteric composition containing 0.5 M 2-phenyl 2-hydroxyethanoic acid and 0.5 M L-citrulline for cosmetic and dermatologic conditions may be formulated as follows.

20 2-Phenyl 2-hydroxyethanoic acid 7.6 g and L-citrulline 8.8 g are dissolved in water 30 ml, and the solution is mixed with 50 g of an oil-in-water emulsion. The lotion thus obtained is made up to 100 ml in volume with more oil-in-water emulsion. The amphoteric composition thus formulated has pH 3.0.



EXAMPLE 24

An amphoteric composition containing 1 M citric acid and 1 M L-arginine for cosmetic conditions and dermatologic disorders may be formulated as follows.

- 5 Citric acid 19.2 g is dissolved in water 50 ml and propylene glycol 10 ml. L-Arginine 17.4 g is added to the solution with stirring until all the crystals are dissolved. More water is added to make a total volume of the solution to 100 ml. The amphoteric composition  
10 thus formulated has pH 3.0. The composition has pH 1.8 if no amphoteric compound is incorporated.

EXAMPLE 25

- A pseudoamphoteric composition containing 1 M citric acid and 1 M creatinine for dermatologic and  
15 cosmetic conditions may be formulated as follows.

- Citric acid 19.2 g and creatinine 11.3 g are dissolved in 40 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The  
20 amphoteric composition thus formulated has pH 3.7.

EXAMPLE 26

An amphoteric composition containing 1 M malic acid and 1 M L-arginine for cosmetic and dermatologic conditions may be formulated as follows.

- 25 2-Hydroxybutanedioic acid (DL-malic acid) 13.4 g and L-arginine 17.4 g are dissolved in water 40 ml and

make a total volume of 100 ml. The amphoteric composition thus formulated for pH 4.6.

EXAMPLE 22

5 A pseudoamphoteric composition containing 0.5 M 2-phenyl 2-hydroxyethanoic acid and 0.5 M creatinine for cosmetic and dermatologic conditions may be formulated as follows.

10 2-Phenyl 2-hydroxyethanoic acid 7.6 g and creatinine 5.7 g are dissolved in 30 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 4.6.

EXAMPLE 23

15 An amphoteric composition containing 0.5 M 2-phenyl 2-hydroxyethanoic acid and 0.5 M L-citrulline for cosmetic and dermatologic conditions may be formulated as follows.

20 2-Phenyl 2-hydroxyethanoic acid 7.6 g and L-citrulline 8.8 g are dissolved in water 30 ml, and the solution is mixed with 50 g of an oil-in-water emulsion. The lotion thus obtained is made up to 100 ml in volume with more oil-in-water emulsion. The amphoteric composition thus formulated has pH 3.0.

EXAMPLE 24

An amphoteric composition containing 1 M citric acid and 1 M L-arginine for cosmetic conditions and dermatologic disorders may be formulated as follows.

5 Citric acid 19.2 g is dissolved in water 50 ml and propylene glycol 10 ml. L-Arginine 17.4 g is added to the solution with stirring until all the crystals are dissolved. More water is added to make a total volume of the solution to 100 ml. The amphoteric composition  
10 thus formulated has pH 3.0. The composition has pH 1.8 if no amphoteric compound is incorporated.

EXAMPLE 25

A pseudoamphoteric composition containing 1 M citric acid and 1 M creatinine for dermatologic and  
15 cosmetic conditions may be formulated as follows.

Citric acid 19.2 g and creatinine 11.3 g are dissolved in 40 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The  
20 amphoteric composition thus formulated has pH 3.7.

EXAMPLE 26

An amphoteric composition containing 1 M malic acid and 1 M L-arginine for cosmetic and dermatologic conditions may be formulated as follows.

25 2-Hydroxybutanedioic acid (DL-malic acid) 13.4 g and L-arginine 17.4 g are dissolved in water 40 ml and

propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.3. The composition has pH 1.8 if no amphoteric compound is incorporated.

#### EXAMPLE 27

10 A pseudoamphoteric composition containing 1 M malic acid and 0.5 M creatinine for cosmetic and dermatologic conditions may be formulated as follows.

DL-Malic acid 13.4 g and creatinine 5.7 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of water is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has pH 3.0. The composition has pH 3.8 when 1 M instead of 0.5 M creatinine is incorporated into the formulation.

#### EXAMPLE 28

20 An amphoteric composition containing 1 M tartaric acid and 1 M L-arginine for cosmetic and dermatologic conditions may be formulated as follows.

2,3-Dihydroxybutanedioic acid (DL-tartaric acid) 15.9 g and L-arginine 17.4 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of water is added

to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.0. The composition has pH 1.7 if no amphoteric compound is incorporated.

5

EXAMPLE 29

A pseudoamphoteric composition containing 1 M tartaric acid and 1 M creatinine for cosmetic and dermatologic conditions may be formulated as follows.

10

DL-Tartaric acid 15.0 g and creatinine 11.3 g are dissolved in 35 ml of water. The solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 3.4.

15

EXAMPLE 30

An amphoteric composition containing 1 M gluconolactone and 0.5 M L-arginine for cosmetic and dermatologic conditions may be formulated as follows.

20

Gluconolactone 17.8 g and L-arginine 8.7 g are dissolved in water 60 ml and propylene glycol 10 ml. After all the crystals have been dissolved sufficient water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.1. The composition has pH 5.9 when 1 M

25

instead of 0.5 M L-arginine is incorporated into the

formulation. If no amphoteric compound is incorporated the pH of the composition is 1.8.

EXAMPLE 31

5 An amphoteric composition containing 1 M gluconolactone and 0.5 M 4-aminobutanoic acid for cosmetic and dermatologic conditions may be formulated as follows.

10 Gluconolactone 17.8 g and 4-aminobutanoic acid 5.2 g are dissolved in water 60 ml and propylene glycol 10 ml. After all the crystals have been dissolved sufficient water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.2.

EXAMPLE 32

15 An amphoteric composition containing 1 M gluconolactone and 1 M dipeptide of Gly-Gly for cosmetic and dermatologic conditions may be formulated as follows.

20 Gluconolactone 17.8 g and glycylglycine 13.2 g are dissolved in water 50 ml and propylene glycol 5 ml. More water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.1

EXAMPLE 33

25 A pseudoamphoteric composition containing 1 M gluconolactone and 0.5 M creatinine for cosmetic

conditions and dermatologic disorders may be formulated as follows.

Gluconolactone 17.8 g and creatinine 5.7 g are dissolved in water 60 ml and propylene glycol 10 ml. More water is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has pH 3.2. The composition has pH 4.8 when 1 M instead of 0.5 M creatinine is incorporated into the formulation.

10

EXAMPLE 34

A pseudoamphoteric composition containing 1 M pyruvic acid and 1 M creatinine for dermatologic and cosmetic conditions may be formulated as follows.

15

2-Ketopropanoic acid (pyruvic acid) 8.8 g and creatinine 11.3 g are dissolved in water 25 ml. The solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.4.

20

EXAMPLE 35

An amphoteric composition containing 0.5 M benzilic acid and 0.5 M L-lysine for cosmetic and dermatologic conditions may be formulated as follows.

25

2,2-Diphenyl 2-hydroxyethanoic acid (benzilic acid) 11.4 g and L-lysine 7.3 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the



crystals have been dissolved sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 4.9. The composition has pH 2.7 if no amphoteric compound is incorporated.

EXAMPLE 36

An amphoteric composition containing 0.5 M benzilic acid and 0.5 M L-histidine for cosmetic and dermatologic conditions may be formulated as follows.

10 Benzilic acid 11.4 g and L-histidine 7.8 g are dissolved in water 40 ml and propylene glycol 20 ml. Ethyl cellulose 2 g is added with stirring, and sufficient amount of ethanol is added to make a total volume of the gel to 100 ml. The amphoteric gel composition thus formulated has pH 5.0.

EXAMPLE 37

A pseudoamphoteric composition containing 0.5 M benzilic acid and 0.5 M creatinine for cosmetic and dermatologic conditions may be formulated as follows.

20 Benzilic acid 11.4 g and creatinine 5.7 g are dissolved in water 40 ml and propylene glycol 20 ml. Sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 4.9.

EXAMPLE 38

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 0.05 % betamethasone dipropionate in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. Betamethasone dipropionate 1 % in ethanol solution 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.2.

EXAMPLE 39

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 0.05% clobetasol propionate in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. Clobetasol propionate 1 % in acetone solution 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.2.

EXAMPLE 40

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 0.1% triamcinolone acetonide in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. Triamcinolone acetonide 2% solution of acetone:ethanol (50:50), 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.2.

EXAMPLE 41

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 0.2 % 5-fluorouracil in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g and creatinine 5.7 g are dissolved in 20 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. 5-Fluorouracil 2% solution of propylene glycol: water (95:5), 10 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.1.

EXAMPLE 42

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxypropanoic acid and 0.05 % betamethasone dipropionate in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxypropanoic acid 4.5 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of a oil-in-water emulsion. Betamethasone dipropionate 1% in ethanol solution 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.1.

EXAMPLE 43

A pseudoamphoteric composition containing in combination 0.5 M hydroxypropanoic acid and 0.05 % clobetasol propionate in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxypropanoic acid 4.5 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. Clobetasol propionate 1% in acetone solution 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.1.

EXAMPLE 44

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxypropanoic acid and 0.1 % triamcinolone acetonide in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxypropanoic acid 4.5 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. Triamcinolone acetonide 2% solution of acetone:ethanol (50:50), 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.1.

EXAMPLE 45

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxypropanoic acid and 0.2 % 5-fluorouracil in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxypropanoic acid 4.5 g and creatinine 5.7 g are dissolved in 20 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. 5-Fluorouracil 2% solution of propylene glycol:water (95:5), 10 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.1.

EXAMPLE 46

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 2% clotrimazole in a cream form for athlete's foot and other fungal infections may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g, clotrimazole 2 g and creatinine 5.7 g are dissolved in water 20 ml and propylene glycol 5 ml, and the solution thus obtained is mixed with enough amount of an oil-in-water emulsion to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.2.

EXAMPLE 47

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 2% erythromycin in solution form for acne may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g, erythromycin 2 g and creatinine 5.7 g are dissolved in water 25 ml, ethanol 40 ml and propylene glycol 15 ml. More water is then added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.2.

EXAMPLE 48

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 1 %

ketoconazole in a cream form for fungal infections may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g, ketoconazole 1 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with enough amount of an oil-in-water emulsion to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.2.

EXAMPLE 49

10 A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxypropanoic acid and 2% clotrimazole in a cream form for fungal infections may be formulated as follows.

15 2-Hydroxypropanoic acid 3.8 g, clotrimazole 2 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with enough amount of an oil-in-water emulsion to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.1.

EXAMPLE 50

20 A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 2% tetracycline in a gel form for dermatologic disorders may be formulated as follows.

25 2-Hydroxyethanoic acid 3.8 g, tetracycline 2 g, creatinine 5.7 g, xantham gum 0.2 g, carbomer-941 1 g,



propylene glycol 5 ml, ethanol 20 ml and enough amount of water are homogenized to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated for acne and oily skin has pH 4.2.

5

EXAMPLE 51

An amphoteric composition containing 0.2 M aleuritic acid and 0.1 M L-lysine in a solution form for cosmetic and dermatologic conditions may be formulated as follows.

10

Aleuritic acid 6.1 g and L-lysine 1.5 g are dissolved in sufficient amount of a solution from ethanol:propylene glycol 80:20 to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 6.4.

15

EXAMPLE 52

A typical composition containing a dimeric form of alpha hydroxyacid in solution for acne, dandruff, and as a skin cleanser may be formulated as follows.

20

Glycolide powder 1.0 g is dissolved in ethanol 89 ml and propylene glycol 10 ml. The composition thus formulated has pH 4.0, and contains 1% active ingredient.

EXAMPLE 53

A typical composition containing a dimeric form of alpha hydroxyacid in ointment for dry skin, psoriasis,

25

eczema, pruritus, wrinkles and other skin changes associated with aging may be formulated as follows.

Glycolide powder 2.0 g is mixed uniformly with petrolatum 66 g and mineral oil 32 g. The composition thus formulated contains 2% active ingredient.

EXAMPLE 54

A typical composition containing a full strength or a high concentration of an alpha hydroxyacid, alpha ketoacid or closely related compound for topical treatments of warts, keratoses, acne, age spots, nail infections, wrinkles and aging related skin changes may be prepared as follows.

If the alpha hydroxyacid, alpha ketoacid or closely related compound at full strength is a liquid form at room temperature such as 2-hydroxypropanoic acid, 2-ketopropanoic acid, methyl 2-ketopropanoate and ethyl 2-ketopropanoate, the compound is directly dispensed as 0.5 to 1 ml aliquots in small vials. If the compound is a solid form at room temperature such as 2-hydroxyethanoic acid and 2-methyl 2-hydroxypropanoic acid, it is first dissolved in minimal amount of an appropriate solvent or solvent system such as water or ethanol and propylene glycol with or without a gelling agent. For example, 2-hydroxyethanoic acid 70 g is dissolved in water 30 ml, and the 70% strength 2-hydroxyethanoic acid thus obtained is

dispensed as 0.5 to 1 ml aliquots in small vials. If a gelling agent is used, methyl cellulose or hydroxyethyl cellulose 1 g may be added to the above solution.

EXAMPLE 55

5        A typical composition containing an intermediate strength of an alpha hydroxyacid, alpha ketoacid or closely related compound for topical treatment of warts, keratoses, acne, nail infections, age spots, wrinkles and aging related skin changes may be prepared  
10 as follows.

2-Hydroxyethanoic acid or 2-ketopropanoic acid 40 g is dissolved in ethanol 54 g and propylene glycol 6 g, and the 40% strength solution thus obtained is dispensed as 5 to 10 ml aliquots in dropper bottles.

15

TEST RESULTS

In order to determine whether amphoteric and pseudoamphoteric compositions of the instant invention were therapeutically effective for various cosmetic conditions and dermatologic disorders, a total of more  
20 than 90 volunteers and patients participated in these studies. Some participating subjects were given two preparations; an amphoteric or pseudoamphoteric composition containing an alpha hydroxyacid or the related compound, and a vehicle placebo. Others were  
25 given multiple preparations containing a known pharmaceutical agent such as a corticosteroid with or

without incorporation of an amphoteric or pseudoamphoteric composition consisting of an alpha hydroxyacid or the related compound of the instant invention. The amphoteric and pseudoamphoteric compositions were formulated according to the Examples described in the previous section.

1. Common dry skin.

Human subjects having ordinary dry skin or with moderate degrees of dry skin as evidenced by dryness, flaking and cracking of the skin were instructed to apply topically the lotion, cream or ointment containing an alpha hydroxyacid or the related compound in amphoteric or pseudoamphoteric composition, on the affected area of the skin. Topical application, two to three times daily, was continued for two to four weeks.

In all the 28 subjects tested, the feeling of the skin dryness disappeared within a week of topical application. The rough and cracked skin became less pronounced and the skin appeared normal and felt smooth after several days of topical treatment. The alpha hydroxyacids and the related compounds which have been found to be therapeutically effective when incorporated into the amphoteric or pseudoamphoteric compositions for dry skin are as follows:

2-hydroxyethanoic acid (glycolic acid), 2-hydroxypropanoic acid (lactic acid), 2-methyl-2-

hydroxypropanoic acid (methyllactic acid), phenyl 2-hydroxyethanoic acid (mandelic acid), phenyl 2-methyl-2-hydroxyethanoic acid (atrolactic acid), 3-phenyl-2-hydroxypropanoic acid (phenyllactic acid), diphenyl 2-hydroxyethanoic acid (benzilic acid), gluconolactone, tartaric acid, citric acid, saccharic acid, malic acid, tropic acid, glucuronic acid, galacturonic acid, gluconic acid, 3-hydroxybutanoic acid, quinic acid, ribonolactone, glucuronolactone, galactonolactone, pyruvic acid, methyl pyruvate, ethyl pyruvate, phenylpyruvic acid, benzoylformic acid and methyl benzoylformate.

The ordinary dry skin conditions, once restored to normal appearing skin, remained improved for some time until causes of dry skin, such as low humidity, cold weather, excessive contact pressure, detergents, soaps, solvents, chemicals, etc., again caused recurrence of the dry skin condition. On continued use it was also found that twice daily topical application of an amphoteric or pseudoamphoteric composition containing an alpha hydroxyacid or the related compound of the instant invention prevented the development of new dry skin lesions.

## 2. Severe dry skin.

In severe dry skin, the skin lesions are different from the ordinary dry skin. A main cause of severe dry skin is inherited genetic defects of the skin. The involved skin is hyperplastic, fissured and has thick adherent scales. The degree of thickening is such that lesions are palpably and visually elevated. The thickened adherent scales cause the surface of involved skin to be markedly rough and uneven. These two attributes of thickness and texture can be quantified to allow objective measurement of degree of improvement from topically applied test materials as follows:

DEGREE OF IMPROVEMENT					
	None ( 0)	Mild ( 1+)	Moderate ( 2+)	Substantial ( 3+)	Complete ( 4+)
Thickness	Highly elevated	Detectable reduction	Readily apparent reduction	Barely elevated	Normal thickness
Texture	Visibly rough	Palpably rough	Uneven but not rough	Slightly uneven	Visibly and palpably smooth

By means of such parameters, degrees of change in lesions can be numerically recorded and comparisons made of one treated site to another.

In order to evaluate the amphoteric and pseudoamphoteric compositions of the instant invention,

a total of 6 patients having severe dry skin conditions were treated with the compositions containing an alpha hydroxyacid or the related compound.

Tested areas were of a size convenient for topical applications, i.e., circles 5 cm in diameter demarcated with a plastic ring of that size inked on a stamp pad. The medicinal lotions or creams were topically applied by the patient in an amount sufficient to cover the treatment sites. Applications were made three times daily and without occlusive dressings. Applications were discontinued at any time when resolutions of the lesion on the treatment area was clinically judged to be complete.

The test results of amphoteric and pseudoamphoteric compositions containing the following alpha hydroxyacids or the related compounds on patients with severe dry skin are summarized as follows:

4+ Effectiveness; glycolic acid, lactic acid, methyllactic acid, mandelic acid, tropic acid, atrolactic acid and pyruvic acid.

3+ Effectiveness; benzilic acid, gluconolactone, malic acid, tartaric acid, citric acid, saccharic acid, methyl pyruvate, ethyl pyruvate, phenyllactic acid, phenylpyruvic acid, glucuronic acid and 3-hydroxybutanoic acid.



2+ Effectiveness; mucic acid, ribonolactone, 2-hydroxydodecanoic acid, quinic acid, benzoylformic acid and methyl benzoylformate.

### 3. Psoriasis.

5 The involved skin in psoriasis is hyperplastic (thickened), erythematous (red or inflamed), and has thick adherent scales. The degree of thickening is such that lesions are elevated up to 1 mm above the surface of adjacent normal skin; erythema is usually an  
10 intense red; the thickened adherent scales cause the surface of involved skin to be markedly rough and uneven. These three attributes of thickness, color and texture can be quantified to allow objective measurement of degree of improvement from topically  
15 applied test materials as follows.

#### DEGREE OF IMPROVEMENT

	None (0)	Mild (1+)	Moderate (2+)	Substantial (3+)	Complete (4+)
THICKNESS	Highly elevated	Detectable reduction	Readily apparent reduction	Barely elevated	Normal thickness
TEXTURE	Visibly rough	Palpably rough	Uneven but not rough	Slightly uneven	Visibly and palpably smooth
COLOR	Intense Red	Red	Dark Pink	Light Pink	Normal Skin Color.

By means of such parameters, degree of improvement in psoriatic lesions can be numerically recorded and comparisons made of one treated site to another.

Patients having psoriasis participated in this study. Amphoteric and pseudoamphoteric compositions containing both an alpha hdyroxyacid or the related compound and a corticosteroid were prepared according to the Examples. Compositions containing only a corticosteroid were also prepared and included in the comparison test. Test areas were kept to minimal size convenient for topical application, i.e., circles approximately 4 cm in diameter. The medicinal compositions were topically applied by the patient in an amount (usually about 0.1 milliliter) sufficient to cover the test site. Applications were made two to three times daily and without occlusive dressings. Test periods usually lasted for two to four weeks. The test results on patients having psoriasis are summarized on the following table.

Topical Effects on Psoriasis of Antipsoriatic Compositions

Compositions*	Therapeutic Effectiveness
Hydrocortisone 2.5% alone	1+
With lactic acid	2+
With glycolic acid	2+

Compositions*		Therapeutic Effectiveness
5	With ethyl pyruvate	2+
	With methyl pyruvate	2+
	With benzilic acid	2+
	With pyruvic acid	2+
	With methyllactic acid	2+
10	Hydrocortisone 17-valerate 0.2% alone	2+
	With lactic acid	3+
	With glycolic acid	3+
	With benzilic acid	3+
	With ethyl pyruvate	3+
15	With methyl pyruvate	3+
	With gluconolactone	3+
	With pyruvic acid	3+
	Betamethasone dipropionate 0.05% alone	3+
	With lactic acid	4+
20	With glycolic acid	4+
	With ethyl pyruvate	4+
	With methyl pyruvate	4+
	With mandelic acid	4+
	With benzilic acid	4+
25	Clobetasol propionate 0.05% alone	3+
	With lactic acid	4+
	With glycolic acid	4+

-----  
 Compositions\*  
 -----

Therapeutic  
 Effectiveness  
 -----

5	With ethyl pyruvate	4+
	With methyl pyruvate	4+
	With methyllactic acid	4+
	With mandelic acid	4+
	With tropic acid	4+
10	With benzilic acid	4+

-----  
 \* Except the "alone" preparations, all others were amphoteric or pseudoamphoteric compositions containing 0.2 to 2M alpha hydroxyacids or related compounds.

15 We have also found that an amphoteric or pseudoamphoteric composition containing an alpha hydroxyacid or the related compound in combination with an antimetabolite agent such as 5-fluorouracil with or without additional incorporation of a corticosteroid is  
 20 therapeutically effective for topical treatment of psoriasis.

4. Eczema.

In a topical treatment of eczema patients, hydrocortisone alone at 2.5% or hydrocortisone 17-  
 25 valerate alone at 0.2% would achieve only 2+ improvement, and betamethasone dipropionate or clobetasol propionate alone at 0.05% would achieve only

a 3+ improvement on all the eczema patients tested. Test results of amphoteric and pseudoamphoteric compositions containing both a corticosteroid and one of the following alpha hydroxyacids or the related compounds are shown as follows:

3+ Effectiveness; hydrocortisone 2.5% or hydrocortisone 17-valerate 0.2% plus lactic acid, glycolic acid, mandelic acid, ethyl pyruvate, gluconolactone, benzilic acid or ribonolactone.

4+ Effectiveness; betamethasone dipropionate or clobetasol propionate 0.05% plus lactic acid, glycolic acid, mandelic acid, ethyl pyruvate, methyl pyruvate, benzilic acid, gluconolactone, citric acid, tartaric acid or methyllactic acid.

#### 5. Oily Skin and Skin Cleanse.

Human subjects having oily skin or blemished skin as well as acne patients having extremely oily skin participated in this study. Amphoteric and pseudoamphoteric compositions containing alpha hydroxyacids or the related compounds were formulated in solution or gel form.

Each participating subject received a solution or a gel preparation containing an alpha hydroxyacid or a related compound in an amphoteric or pseudoamphoteric composition. The participating subjects were

instructed to apply topically the solution or gel medication on the affected areas of forehead or other part of the face. Three times daily applications were continued for 2 to 6 weeks.

5           The degree of improvement of oily skin as well as the rate of improvement of acne lesions were clinically evaluated. Most participants reported that oiliness of skin disappeared within one to two weeks of topical administration, and the skin so treated became smooth and soft. Many participating subjects preferred gel preparations than solution compositions. It was found that all the participants showed substantial improvements on oily skin and acne lesions by six weeks of topical administration of amphoteric or pseudoamphoteric compositions containing alpha hydroxyacids or the related compounds of the instant invention.

10           Those alpha hydroxyacids and the related compounds which have been found to be therapeutically effective for oily skin and as skin cleansers include: benzilic acid, glycolic acid, lactic acid, methyllactic acid, mandelic acid, pyruvic acid, ethyl pyruvate, methyl pyruvate, tropic acid, malic acid, gluconolactone, 3-hydroxybutanoic acid, glycolide and polyglycolic acid.

15           As a skin cleanser for oily skin or acne-prone skin, the amphoteric or pseudoamphoteric composition

containing an alpha hydroxyacid or the related compound may also be incorporated with other dermatologic agents. For example, an amphoteric gel composition may consist of both an alpha hydroxyacid and erythromycin or tetracycline.

#### 6. Acne

Amphoteric and pseudoamphoteric compositions containing alpha hydroxyacids or the related compounds of the instant invention in a solution or gel form were provided to patients having comedogenic and/or papulopustular lesions of acne. Each participating patient was instructed to apply topically the composition on the involved areas of the skin such as forehead, face and chest. Three times daily administration was continued for 6 to 12 weeks.

The degree and rate of improvement on acne lesions were clinically evaluated. It was found that acne lesions consisting mainly of comedones improved substantially after 6 to 8 weeks of topical administration with the amphoteric or the pseudoamphoteric composition containing an alpha hydroxyacid or the related compound. The time for complete clearing of comedogenic acne treated with the amphoteric or pseudoamphoteric composition of the instant invention varied from 6 to 12 weeks.



As a topical treatment for papulopustular and/or pustular acne the amphoteric or pseudoamphoteric composition containing an alpha hydroxyacid or the related compound may incorporate in addition an  
5 antiacne agent. The antiacne agents include antibiotics such as erythromycin, tetracycline, clindamycin, meclocycline and minocycline, and retinoids such as retinoic acid. Such combination  
10 compositions have been found to be therapeutically more effective for topical treatment of severe acne.

#### 7. Age Spots

Many small and large discolored lesions, commonly called age spots on the face and the back of the hands are benign keratoses, if they are not variants of  
15 actinic keratoses. Very few of such age spots are true lentigines, therefore alpha hydroxyacids and the related compounds may be effective in eradicating most age spots without concurrent use of skin bleaching agents such as hydroquinone and monobenzene. However,  
20 additional beneficial effects have been found when a skin bleaching agent such as hydroquinone or monobenzene is also incorporated into the compositions of the instant invention for age spots involving pigmented lesions.

Amphoteric and pseudoamphoteric compositions containing alpha hydroxyacids or the related compounds, with or without incorporation of hydroquinone were provided to volunteer subjects and patients having age  
5 spot keratoses, melasma, lentigines and/or other pigmented lesions. Each participating subject received two products, i.e., with or without the addition of 2% hydroquinone to the amphoteric or pseudoamphoteric composition containing an alpha hydroxyacid or the  
10 related compound.

The volunteer subjects and patients were instructed to apply topically one medication on one side of the body such as left side of the face or on the back of the left hand, and the other medication on  
15 the other side of the body such as on right side of the face or on the back of the right hand. Specific instructions were given to the participating subjects that the medications were applied three times daily to the lesions of age spot keratoses, melasmas, lentigines  
20 and/or other pigmented lesions. Clinical photos were taken of participating subjects before the initiation of the topical treatment and every 4 weeks during the course of treatment.

At the end of 4 to 8 weeks, improvement of age  
25 spot keratoses was clinically discernible. After 4 to 6 months of topical treatment, substantial improvement

of age spot keratoses occurred in the majority of subjects tested. Complete eradication of age spot keratoses occurred after 6 to 9 months of topical administration with the amphoteric or pseudoamphoteric compositions of the instant inventions.

Amphoteric or pseudoamphoteric compositions containing both an alpha hydroxyacid or the related compound and hydroquinone were judged to be more effective in eradicating pigmented age spots, melasma, lentigines and other pigmented lesions.

The alpha hydroxyacids and the related compounds which have been found to be therapeutically effective for age spots with or without combination with hydroquinone include glycolic acid, lactic acid, methyllactic acid, mandelic acid, pyruvic acid, methyl pyruvate, ethyl pyruvate, benzilic acid, gluconolactone, malic acid, tartaric acid, citric acid and tropic acid. For flat or slightly elevated seborrheic keratoses on the face and/or the back of the body, amphoteric or pseudoamphoteric compositions containing higher concentrations of alpha hydroxyacids or the related compounds have been found to be effective in eradicating such lesions.

Actinic keratoses may be successfully treated with amphoteric or pseudoamphoteric compositions containing alpha hydroxyacids or the related compounds in

combination with an antimetabolite agent such as 5-fluorouracil.

#### 8. Warts.

5       Eradications of common warts by topical  
application of amphoteric or pseudoamphoteric  
compositions require higher than usual concentrations  
of alpha hydroxyacids or the related compounds in the  
formulations. The amphoteric or pseudoamphoteric  
10       compositions were formulated as a liquid or light gel  
form, and dispensed usually as 0.5-1 ml aliquots in  
small vials.

15       Topical applications were made discreetly to wart  
lesions by adult patients or by responsible adult  
family members. For ordinary usual warts of hands,  
fingers, palms and soles topical applications were made  
2 to 4 times daily, and were continued for 2 to 6  
20       weeks. Generally, the overlying stratum corneum of the  
wart lesion change in appearance after several weeks  
topical application of the composition. In most cases,  
the wart lesion simply fell off. The skin then healed  
normally without forming any scars.

25       We have also found that when a dermatologic agent  
such as 5-fluorouracil is incorporated into the  
amphoteric or pseudoamphoteric compositions containing  
alpha hydroxyacids or the related compounds, the

medications have been very effective for topical treatment of warts without using higher concentrations of alpha hydroxyacids or the related compounds.

5 The alpha hydroxyacids and the related compounds which have been found to be therapeutically effective for topical treatment of warts with or without incorporation of 5-fluorouracil include glycolic acid, lactic acid, pyruvic acid, ethyl pyruvate, methyl pyruvate and mandelic acid.

10 Topical formulations and compositions containing specific alpha hydroxyacids, alpha ketoacids or the related compounds at full strengths or high to intermediate concentrations prepared according to Examples 54 and 55, without utilizing amphoteric or  
15 pseudoamphoteric systems, have also been tested for ordinary warts of the hands, fingers, palms and soles. Participating patients have been advised to apply a small drop of the medication with a toothpick or a fine  
20 caliber brush to the center of a wart lesion only. Prescribed applications have been 3 to 6 times daily, and are continued until the patient feels pain.

For the more rough-surfaced wart, the duration of application has been as short as one or a few days. For lesions with more compact, less permeable stratum  
25 corneum, the time to experience pain has been longer. Frequency and duration of applications have been

modified according to other clinical responses and reactions of lesions, and the patient or responsible family member is instructed accordingly.

For example, some clinical manifestations other than pain have also been used as a signal to interrupt application. These manifestations have included distinct blanching of the lesions or distinct peripheral erythema. Very often, discomfort is the usual signal of clinical reactions.

Generally, the overlying stratum corneum of the wart lesions became loose, and the whole wart lesion simply fell off. The skin then healed normally without forming any scars.

#### 9. Athlete's Foot and Nail Infections

Amphoteric and pseudoamphoteric compositions containing both an antifungal agent and one of the alpha hydroxyacids or the related compounds were provided to patients having frequent recurrence of fungal infections involving the foot. The antifungal agents include clotrimazole, miconazole, ketoconazole and griseofulvin. When both feet but not toe nails were involved in the infection, the patients were instructed to apply topically the compositions of the instant invention on the left foot, and a brand-name antifungal product on the right foot. Three times

daily applications were continued for one to four weeks. The degree and rate of improvement on skin lesions were clinically evaluated, and comparison was made one side of the body against the other. It was found that the skin lesions improved much faster with the amphoteric or pseudoamphoteric compositions containing both the antifungal agent and the alpha hydroxyacid or the related compound. The alpha hydroxyacids or the related compounds seemed to enhance the efficacies of the antifungal agents, and also to eliminate the discomforts such as itching, tingling, burning and irritation due to fungal infections. When toe nails were not involved the infected skin generally healed within one to two weeks from topical application of the amphoteric or pseudoamphoteric composition containing both an antifungal agent and an alpha hydroxyacid or the related compound.

Fungal infections of the nails are very difficult to treat, because antifungal products to date are not therapeutically effective for topical treatment of nails. One of the reasons is that most antifungal drugs have not been formulated as bioavailable forms in the commercial products. When tow nails were involved in the infections, patients were provided with amphoteric or pseudoamphoteric compositions containing in combination an antifungal agent and an alpha hydro-



xyacid or an alpha ketoacid at higher concentrations ranging from 20 to 99%, dispensed as 1-2 ml aliquots in small vials. The patients were instructed to apply topically the compositions discreetly to the infected nail surface by means of a fine calibre paint brush. the technique was the same as for application of nail polish, that is careful avoidance of contact with lateral nail folds or any peri-ungual skin. Once or twice daily applications were continued for 2 to 8 weeks.

As mentioned above, while brand-name antifungal products are usually not effective against fungus infections within or underneath the nail, it was found that the amphoteric or pseudoamphoteric compositions containing an antifungal agent and an alpha hydroxyacid or alpha ketoacid were therapeutically effective in eradicating fungal infections of the nails. Such treatment may cause in some instances the treated nail plate to become loose and eventually fell off from the nail bed. This happened quite naturally without any feeling of pain nor bleeding, and the skin lesion healed quickly with normal growth of a new nail.

#### 10. Wrinkles

Wrinkles of skin may be due to natural aging and/or sun damage. Most fine wrinkles on the face are

due to natural or innate aging, while coarse wrinkles on the face are the consequence of actinic or sun damage. Although the real mechanism of wrinkles formation in the skin is still unknown, it has been

5 shown that visible fine wrinkles are due to diminution in the number and diameter of elastic fibers in the papillary dermis, and also due to atrophy of dermis as well as reduction in subcutaneous adipose tissue. Histopathology and electron microscopy studies indicate

10 that coarse wrinkles are due to excessive deposition of abnormal elastic materials in the upper dermis and thickening of the skin. At present there are no commercial products which have been found to be therapeutically effective for topical eradication of

15 wrinkles, although retinoic acid (tretinoin) has been shown to be beneficial for sun damaged skin.

In order to determine whether the amphoteric or pseudoamphoteric composition containing the alpha hydroxyacids, alpha ketoacids or the related compounds

20 are therapeutically effective for wrinkles, patients and volunteer subjects participated in this study. The participants were instructed to apply the formulations of the instant invention twice daily on areas of facial wrinkles for 4 to 12 months. All participants were

25 told to avoid sun exposure, and to use sunscreen products if exposure to sunlight was unavoidable.

Photographs of each side of the face for each participant were taken at the beginning of the study and repeated at one to three-month intervals. The participants were asked not to wear any facial make-up at the time of each office visit. Standardized photographic conditions were used including the use of same lot of photographic film, the same light source at two feet from the face, aimed at a locus on the frontal aspect of each cheek. Each time photographs were taken with camera aimed perpendicular to the cheek. At the end of study twenty two participants had been entered into the study for at least four months. Clinical evaluations and review of photographs have revealed substantial reductions in facial wrinkles of the temporal region and cheek area on at least one side of the face in eighteen cases. Degree of improvement and reduction in wrinkles has been evaluated and determined to be mild to moderate in six participants but very substantial in twelve participants.

The alpha hydroxyacids, alpha ketoacids and other related compounds including their lactone forms which may be incorporated into the amphoteric and pseudoamphoteric compositions for cosmetic conditions and dermatologic disorders such as dry skin, acne, age spots, keratoses, warts and skin wrinkles or in

combination with other dermatologic agents to enhance therapeutic effects include the following:

(1) Alkyl Alpha Hydroxyacids

2-Hydroxyethanoic acid (Glycolic acid), 2-  
 5 Hydroxypropanoic acid (Lactic acid), 2-Methyl 2-  
 hydroxypropanoic acid (Methylactic acid), 2-  
 Hydroxybutanoic acid, 2-Hydroxypentanoic acid, 2-  
 Hydroxyhexanoic acid, 2-Hydroxyheptanoic acid, 2-  
 Hydroxyoctanoic acid, 2-Hydroxynonanoic acid, 2-  
 10 Hydroxydecanoic acid, 2-Hydroxyundecanoic acid, 2-  
 Hydroxydodecanoic acid (Alpha hydroxylauric acid), 2-  
 Hydroxytetradecanoic acid (Alpha hydroxymyristic acid),  
 2-Hydroxyhexadecanoic acid (Alpha hydroxypalmitic  
 acid), 2-Hydroxyoctadecanoic acid (Alpha hydroxystearic  
 15 acid), 2-Hydroxyeicosanoic acid (Alpha  
 hydroxyarachidonic acid).

(2) Aralkyl And Aryl Alpha Hydroxyacids

2-Phenyl 2-hydroxyethanoic acid (Mandelic acid),  
 2,2-Diphenyl 2-hydroxyethanoic acid (Benzilic acid), 3-  
 20 Phenyl 2-hydroxypropanoic acid (Phenyllactic acid), 2-  
 Phenyl 2-methyl 2-hydroxyethanoic acid (Atrolactic  
 acid), 2-(4'-Hydroxyphenyl) 2-hydroxyethanoic acid, 2-  
 (4'-Chlorophenyl) 2-hydroxyethanoic acid, 2-(3'-Hydroxy-  
 4'-methoxyphenyl) 2-hydroxyethanoic acid, 2-(4'-  
 25 Hydroxy-3'-methoxyphenyl) 2-hydroxyethanoic acid, 3-  
 (2'-Hydroxyphenyl) 2-hydroxypropanoic acid, 3-(4'-

Hydroxyphenyl) 2-hydroxypropanoic acid, 2-(3',4'-Dihydroxyphenyl) 2-hydroxyethanoic acid.

(3) Polyhydroxy Alpha Hydroxyacids

2,3-Dihydroxypropanoic acid (Glyceric acid),  
 5 2,3,4-Trihydroxybutanoic acid (Isomers; erythronic acid, threonic acid), 2,3,4,5-Tetrahydroxypentanoic acid (Isomers; ribonic acid, arabinoic acid, xylonic acid, lyxonic acid), 2,3,4,5,6-Pentahydroxyhexanoic acid (Isomers; aldonic acid, altronic acid, gluconic  
 10 acid, mannoic acid, gulonic acid, idonic acid, galactonic acid, talonic acid),. 2,3,4,5,6,7-Hexahydroxyheptanoic acid (Isomers; glucoheptonic acid, galactoheptonic acid, etc.)

(4) Polycarboxylic Alpha Hydroxyacids

15 2-Hydroxypropane-1,3-dioic acid (Tartronic acid), 2-Hydroxybutane-1,4-dioic acid (Malic acid), 2,3-Dihydroxybutane-1,4-dioic acid (Tartaric acid), 2-Hydroxy-2-carboxypentane-1,5-dioic acid (Citric acid), 2,3,4,5-Tetrahydroxyhexane-1,6-dioic acid (Isomers;  
 20 saccharic acid, mucic acid, etc.)

(5) Alpha Hydroxyacid Related Compounds

Ascorbic acid, quinic acid, isocitric acid, tropic acid, 3-chlorolactic acid, trethocanic acid, cerebronic acid, citramalic acid, agaricic acid, 2-hydroxynervonic  
 25 acid and aleuritic acid.

## (6) Alpha Ketoacids And Related Compounds

2-Ketoethanoic acid (Glyoxylic acid), Methyl 2-ketoethanoate, 2-Ketopropanoic acid (Pyruvic acid), Methyl 2-ketopropanoate (Methyl pyruvate), Ethyl, 2-ketopropanoate (Ethyl pyruvate), Propyl 2-ketopropanoate (Propyl pyruvate), 2-Phenyl-2-ketoethanoic acid (Benzoylformic acid), Methyl 2-phenyl-2-ketoethanoate (Methyl benzoylformate), Ethyl 2-phenyl-2-ketoethanoate (Ethyl benzoylformate), 3-Phenyl-2-ketopropanoic acid (Phenylpyruvic acid), Methyl 3-phenyl-2-ketopropanoate (Ethyl phenylpyruvate), 2-Ketobutanoic acid, 2-Ketopentanoic acid, 2-Ketohexanoic acid, 2-Ketoheptanoic acid, 2-Ketooctanoic acid, 2-Ketododecanoic acid, Methyl 2-ketooctanoate

The amphoteric and pseudoamphoteric compounds which may be incorporated into the compositions of the instant invention for cosmetic and dermatologic conditions include amino acids, peptides, polypeptides, proteins and the like compounds such as creatinine and creatine.

The dimeric and polymeric forms of alpha hydroxyacids and the related compounds which may be incorporated into the compositions of the instant invention include acyclic esters and cyclic ester; for example, glycolyl glycollate, lactyl lactate,

glycolide, lactide, polyglycolic acid and polylactic acid.

5 The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The present embodiments are therefore to be considered in all respects as illustrative and not restrictive, the scope of the invention being indicated by the appended claims and all changes which come within the meaning and  
10 equivalency of the claims are therefore intended to be embraced therein.



THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A composition comprising:

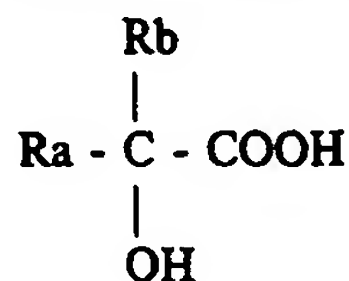
(a) an amphoteric or pseudoamphoteric agent;

(b) a cosmetic agent or a pharmaceutical agent; and

5 (c) an alpha hydroxyacid, an alpha ketoacid or a related compound present in a therapeutically effective amount in a topically acceptable vehicle for topical treatment of cosmetic conditions or dermatologic disorders,

10 said amphoteric or pseudoamphoteric agent being at least one member selected from the group consisting of dipeptides, creatine, aminoaldonic acids, aminouronic acids, lauryl aminopropylglycine, aminoaldaric acids, neuraminic acid, desulfated heparin, deacetylated hyaluronic acid, hyalobiuronic acid, chondrosine, deacetylated chondroitin, cocoamphoglycine, cocoamphopropionate, cocoamphopropylsulfonate, phosphatidyl ethanolamine, glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, cystine, methionine, asparagine, glutamine, arginine, lysine, creatinine, 5-hydroxylysine, 15 histidine, phenylalanine, tyrosine, tryptophan, 3-hydroxyproline, 4-hydroxyproline, proline, homocysteine, homocystine, homoserine, ornithine, citrulline, phosphatidylserine, and sphingomyelin;

20 said alpha hydroxyacid being at least one member selected from the group consisting of alkyl alpha hydroxyacid, aralkyl and aryl alpha hydroxyacid, polyhydroxy alpha hydroxyacid and polycarboxylic alpha hydroxyacid having the following chemical structure:



25 wherein Ra and Rb are H, F, Cl, Br, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric and non-isomeric, straight or branched chain, having 1 to 25 carbon atoms, or cyclic from having 5 or 6 ring members, and in addition Ra and Rb may carry OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms, said alpha hydroxyacid

existing as a free acid or lactone form, or in salt form with an organic base or an inorganic alkali, and as stereoisomers as D, L, and DL forms when Ra and Rb are not identical;

said alpha ketoacid being at least one member selected from a group of compounds represented by the following chemical structure:



wherein Ra is H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain, having 1 to 25 carbon atoms, or cyclic form having 5 or 6 ring members, and in addition Ra may carry F, Cl, Br, I, OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms, said alpha ketoacid existing as a free acid or in a salt form with an organic base or an inorganic alkali; and

said related compound being at least-one member selected from the group consisting of ascorbic acid, quinic acid, isocitric acid, tropic acid, trethocanic acid, 3-chlorolactic acid, cerebronic acid, citramalic acid, agaricic acid, 2-hydroxynervonic acid, aleuritic acid and pantoic acid.

2. The composition of claim 1, wherein said amphoteric or pseudoamphoteric agent is at least one member selected from the group consisting of glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, cystine, methionine, asparagine, glutamine, arginine, lysine, 5-hydroxylysine, histidine, phenylalanine, tyrosine, tryptophan, 3-hydroxyproline, 4-hydroxyproline, proline, homocysteine, homocystine, homoserine, ornithine, citrulline, creatine, aminoaldonic acids, aminouronic acids, aminoaldaric acids, lauryl aminopropylglycine, neuraminic acid, desulfated heparin, deacetylated hyaluronic acid, hyalobiuronic acid, chondrosine, deacetylated chondroitin, creatinine, 2-aminobutanoic acid, 4-aminobutanoic acid, 2-amino-2-methylpropanoic acid, 2-methyl-3-aminopropanoic acid, theanine, phenylglycine, canavanine, canaline, 4-hydroxyarginine, 4-hydroxyornithine, 2,4-

diaminobutanoic acid, 2,3-diaminopropanoic acid, 2,6-diaminopimelic acid, 2-amino-3-phenylbutanoic acid, taurine, methionine sulfoxide, methionine sulfone, 3,5-diiodotyrosine, thyroxine, moniodotyrosine, pipecolic acid, 4-aminopipecolic acid, 4-methylproline, glycylglycine, carnosine, anserine, ophidine, homocarnosine,  $\beta$ -alanyllysine,  $\beta$ -alanylarginine, glutathione, ophthalmic acid, norophthalmic acid, cocoamphoglycine, cocoamphopropionate, cocoamphopropylsulfonate, phosphatidylethanolamine, phosphatidylserine, and sphingomyelin.

3. The composition of claim 1, wherein said alkyl alpha hydroxyacid is at least one member selected from the group consisting of 2-hydroxyethanoic acid (glycolic acid), 2-hydroxypropanoic acid (lactic acid), 2-methyl 2-hydroxypropanoic acid (methyllactic acid), 2-hydroxybutanoic acid, 2-hydroxypentanoic acid, 2-hydroxyhexanoic acid, 2-hydroxyheptanoic acid, 2-hydroxyoctanoic acid, 2-hydroxynonanoic acid, 2-hydroxydecanoic acid, 2-hydroxyundecanoic acid, 2-hydroxydodecanoic acid (alpha hydroxylauric acid), 2-hydroxytetradecanoic acid (alpha hydroxymyristic acid), 2-hydroxyhexadecanoic acid (alpha hydroxypalmitic acid), 2-hydroxyoctadecanoic acid (alpha hydroxystearic acid) and 2-hydroxyeicosanoic acid (alpha hydroxyarachidonic acid).

4. The composition of claim 1, wherein said aralkyl and aryl alpha hydroxyacid is selected from the group consisting of 2-phenyl 2-hydroxyethanoic acid (mandelic acid), 2,2-diphenyl 2-hydroxyethanoic acid (benzilic acid), 3-phenyl 2-hydroxypropanoic acid (phenyllactic acid), 2-phenyl 2-methyl 2-hydroxyethanoic acid (atrolactic acid), 2-(4'-hydroxyphenyl) 2-hydroxyethanoic acid, 2-(4'-chlorophenyl) 2-hydroxyethanoic acid, 2-(3'-hydroxy-4'-methoxyphenyl) 2-hydroxyethanoic acid, 2-(4'-hydroxy-3'-methoxyphenyl) 2-hydroxyethanoic acid, 3-(2'-hydroxyphenyl) 2-hydroxypropanoic acid, 3-(4'-hydroxyphenyl) 2-hydroxypropanoic acid and 2-(3',4'-dihydroxyphenyl) 2-hydroxyethanoic acid.

5. The composition of claim 1, wherein said polyhydroxy alpha hydroxyacid and polycarboxylic alpha hydroxyacid is at least one member selected from the group consisting

of 2,3-Dihydroxypropanoic acid (Glyceric acid), 2,3,4-Trihydroxybutanoic acid and Isomers erythronic acid and threonic acid, 2,3,4,5-Tetrahydroxypentanoic acid and Isomers ribonic acid, arabinoic acid, xylonic acid and lyxonic acid, 2,3,4,5,6-Pentahydroxyhexanoic acid and Isomers allonic acid, altronic acid, gluconic acid, mannoic acid, gulonic acid, idonic acid, galactonic acid and talonic acid, 2,3,4,5,6,7 Hexahydroxyheptanoic acid and Isomers glucoheptonic acid and galactoheptonic acid, 2-Hydroxypropane-1,3-dioic acid (Tartronic acid), 2-Hydroxybutane-1,4-dioic acid (Malic acid), 2,3-Dihydroxybutane-1,4-dioic acid (Tartaric acid), 2-Hydroxy-2-carboxypentane-1,5-dioic acid (citric acid), 2,3,4,5-Tetrahydroxyhexane-1,6-dioic acid and Isomers saccharic acid and mucic acid, or lactone forms gluconolactone, galactonolactone, glucuronolactone, galacturonolactone, gulonolactone, ribonolactone, saccharic acid lactone, pantoyllactone, glucoheptonolactone, mannolactone and galactoheptonolactone.

6. The composition of claim 1, wherein said alpha ketoacid is at least one member selected from the group consisting of 2-Ketoethanoic acid (Glyoxylic acid), 2-Ketopropanoic acid (Pyruvic acid), 2-Phenyl-2-ketoethanoic acid (Benzoylformic acid), 3-Phenyl-2-ketopropanoic acid (Phenylpyruvic acid), 2-Ketobutanoic acid, 2-Ketopentanoic acid, 2-Ketohexanoic acid, 2-Ketoheptanoic acid, 2-Ketooctanoic acid and 2-Ketododecanoic acid.

7. The composition of any one of claims 1 to 6, for topical treatment of cosmetic conditions or dermatologic disorders wherein said cosmetic conditions, and dermatologic disorders are selected from the group consisting of dry skin, zerosis, ichthyosis, dandruff, brownish spots, keratoses, melasma, lentigines, age spots, liver spots, pigmented spots, wrinkles, blemishes, skin lines, oily skin, acne, warts, eczema, pruritic skin, psoriasis, inflammatory dermatoses, disturbed keratinization, skin changes associated with aging, nail or skin requiring cleansers, conditioning or treatment, and hair or scalp requiring shampooing or conditioning.

8. The composition of any one of claims 1-7, wherein the cosmetic agent or pharmaceutical agent is selected from the group consisting of cosmetic or pharmaceutical agent is selected from the group consisting of clotrimazole, ketoconazole, miconazole, griseofulvin, hydroxyzine, diphenhydramine, pramoxine, lidocaine, procaine, mepivacaine, hydroquinone, monobenzene, erythromycin, tetracycline, clindamycin, meclocycline, minocycline, naproxen, ibuprofen, theophylline, cromolyn, albuterol, retinoic acid, 13-cis retinoic acid, hydrocortisone, hydrocortisone 21-acetate, hydrocortisone 17-valerate, hydrocortisone 17-butyrate, betamethasone dipropionate, triamcinolone acetonide, fluocinonide, clobetasol propionate, benzoyl peroxide, crotamiton, propranolol, promethazine, vitamin A palmitate, vitamin A acetate, and vitamin E acetate.

9. The composition of any one of claims 1-7, wherein the cosmetic agent or pharmaceutical agent is selected from the group consisting of agents that improve or eradicate age spots, keratoses and wrinkles; analgesics; anesthetics; antiacne agents; antibacterials; antiyeast agents; antifungal agents; antiviral agents; antidandruff agents; antidermatitis agents; antipruritic agents; antiemetics; antimotionsickness agents; antiinflammatory agents; antihyperkeratolytic agents; antidry skin agents; antiperspirants; antipsoriatic agents; antiseborrheic agents; hair conditioners and hair treatment agents; antiaging and antiwrinkle agents; antiasthmatic agents and bronchodilators; sunscreen agents; antihistamine agents; skin lightening agents; depigmenting agents; vitamins; corticosteroids; tanning agents, hormones; retinoids; topical cardiovascular agents or dermatologicals.

10. A composition comprising an acyclic ester of hydroxyacids, present in a therapeutically effective amount in a pharmaceutically acceptable vehicle for topical treatment of cosmetic conditions or dermatologic disorders wherein,

said acyclic ester of hydroxyacids is at least one member having the following  
5 structure:



wherein Ra and Rb are H, alkyl, aralkyl or aryl group of saturated or unsaturated,  
isomeric or non-isomeric, straight or branched chain, having 1 to 25 carbon atoms, or cyclic  
form having 5 or 6 ring members, and n is 2 or any number up to 200; Ra and Rb in  
10 monomer unit 2 through 200 may be the same or the different groups from that in monomer  
unit 1; the hydrogen atom in Ra and Rb may be substituted by a halogen atom or a radical of  
lower alkyl, aralkyl, aryl or alkoxy of saturated or unsaturated, isomeric or non-isomeric,  
straight or branched chain, having 1 to 9 carbon atoms, or cyclic form having 5 to 6 ring  
members, and the acyclic esters of hydroxyacids being present as a free acid, ester or in a  
15 salt form with an organic base or inorganic alkali in a pharmaceutically acceptable vehicle,  
and

wherein said acyclic esters of hydroxyacids are formed by the reaction of two or more  
molecules of hydroxycarboxylic acid, wherein one of the molecules is selected from the  
group consisting of glycolic acid, lactic acid, mandelic acid, atrolactic acid, citric acid,  
20 phenyllactic acid, benzilic acid, tropic acid, trethocanic acid, aleuritic acid, glyceric acid,  
gluconic acid and gluconolactone, galactonic acid and galactonolactone, glucuronic acid and  
glucuronolactone, ribonic acid and ribonolactone, galacturonic acid and galacturonolactone,  
ascorbic acid, gulonic acid and gulonolactone, glucoheptonic acid and glucoheptonolactone,  
malic acid, citramalic acid, tartronic acid, agaricic acid, isocitric acid, tartaric acid, mucic  
25 acid and saccharic acid.

11. The composition of claim 10, comprising acyclic esters of hydroxyacids  
formed by the reaction of two or more molecules of hydroxycarboxylic acid, wherein one of  
the molecules is glycolic acid.



12. The composition of claim 10, comprising acyclic esters of hydroxyacids formed by the reaction of two or more molecules of hydroxycarboxylic acid, wherein one of the molecules is mandelic acid.

13. The composition of claim 10, comprising acyclic esters of hydroxyacids formed by the reaction of two or more molecules of hydroxycarboxylic acid, wherein one of the molecules is atrolactic acid.

14. The composition of claim 10, comprising acyclic esters of hydroxyacids formed by the reaction of two or more molecules of hydroxycarboxylic acid, wherein one of the molecules is citric acid.

15. The composition of claim 10, comprising acyclic esters of hydroxyacids formed by the reaction of two or more molecules of hydroxycarboxylic acid, wherein one of the molecules is phenyllactic acid.

16. The composition of claim 10, comprising acyclic esters of hydroxyacids formed by the reaction of two or more molecules of hydroxycarboxylic acid, wherein one of the molecules is benzilic acid.

17. The composition of claim 10, comprising acyclic esters of hydroxyacids formed by the reaction of two or more molecules of hydroxycarboxylic acid, wherein one of the molecules is selected from the group consisting of tropic acid, trethocanic acid and aleuritic acid.

18. The composition of claim 10, comprising acyclic esters of hydroxyacids formed by the reaction of two or more molecules of hydroxycarboxylic acid, wherein one of the molecules is selected from the group consisting of glyceric acid, gluconic acid and gluconolactone, galactonic acid and galactonolactone, glucuronic acid and glucuronolactone,



- 5    ribonic acid and ribonolactone, galacturonic acid and galacturonolactone, ascorbic acid, gulonic acid and gulonolactone, glucoheptonic acid and glucoheptonolactone.

19.    The composition of claim 10, comprising acyclic esters of hydroxyacids formed by the reaction of two or more molecules of hydroxycarboxylic acid, wherein one of the molecules is selected from the group consisting of malic acid, citric acid, citramalic acid, tartronic acid, agaricic acid and isocitric acid.

20.    The composition of claim 10, comprising acyclic esters of hydroxyacids formed by the reaction of two or more molecules of hydroxycarboxylic acid, wherein one of the molecules is selected from the group consisting of tartaric acid, mucic acid and saccharic acid.

21.    The composition of claim 10, comprising acyclic esters of hydroxyacids formed by the reaction of two or more molecules of hydroxycarboxylic acid, wherein one of the molecules is lactic acid.

22.    The composition of claim 10, wherein said acyclic esters of hydroxyacids are selected from the group consisting of glycolyl glycollate, lactyl lactate, mandelyl mandellate, atrolactyl atrolactate, phenyllactyl phenyllactate, benzyl benzillate, glycolyl lactate, lactyl glycollate, triglycolic acid, trilactic acid, polyglycolic acid or polylactic acid.

23.    The composition of any one of claims 10-22, wherein the composition further comprises an amphoteric or pseudoamphoteric agent comprising at least one member selected from the group consisting of dipeptide, creatine, aminoaldonic acid, aminouronic acid, lauryl aminopropylglycine, aminoaldaric acid, neuraminic acid, desulfated heparin, deacetylated  
5    hyaluronic acid, hyalobiuronic acid, chondrosine, deacetylated chondroitin, creatinine, cocoamphoglycine, cocoamphopropionate, cocoamphopropylsulfonate, phosphatidyl ethanolamine, glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine,

cystine, methionine, asparagine, glutamine, arginine, lysine, 5-hydroxylysine, histidine, phenylalanine, tyrosine, tryptophan, 3-hydroxyproline, 4-hydroxyproline, proline,  
10 homocysteine, homocystine, homoserine, ornithine, citrulline, phosphatidylserine, and sphingomyelin.

24. The composition of any one of claims 10-23, , further comprising a cosmetic agent or a pharmaceutical agent for topical treatment of dermatological disorders.

25. The composition of claim 24, wherein the cosmetic agent or pharmaceutical agent is selected from the group consisting of cosmetic or pharmaceutical agent is selected from the group consisting of clotrimazole, ketoconazole, miconazole, griseofulvin, hydroxyzine, diphenhydramine, pramoxine, lidocaine, procaine, mepivacaine, hydroquinone,  
5 monobenzene, erythromycin, tetracycline, clindamycin, meclocycline, minocycline, naproxen, ibuprofen, theophylline, cromolyn, albuterol, retinoic acid, 13-cis retinoic acid, hydrocortisone, hydrocortisone 21-acetate, hydrocortisone 17-valerate, hydrocortisone 17-butyrate, betamethasone dipropionate, triamcinolone acetonide, fluocinonide, clobetasol propionate, benzoyl peroxide, crotamiton, propranolol, promethazine, vitamin A palmitate  
10 and vitamin E acetate.

26. The composition of claim 24, wherein said cosmetic or pharmaceutical agent is selected from the group consisting of agents that improve or eradicate age spots, keratoses and wrinkles; analgesics; anesthetics; antiacne agents; antibacterials; antiyeast agents; antifungal agents; antiviral agents; antidandruff agents; antidermatitis agents; antipruritic  
5 agents; antiemetics; antimotionsickness agents; antiinflammatory agents; antihyperkeratolytic agents; antidry skin agents; antiperspirants; antipsoriatic agents; antiseborrheic agents; hair conditioners and hair treatment agents; antiaging and antiwrinkle agents; antiasthmatic agents and bronchodilators; sunscreen agents; antihistamine agents; skin lightening agents; depigmenting agents; vitamins; corticosteroids; tanning agents; hormones; retinoids; topical  
10 cardiovascular agents or dermatologicals.

27. The composition of claim 10, wherein said cosmetic conditions and dermatologic disorders are selected from the group consisting of dry skin, zerosis, ichthyosis, dandruff, brownish spots, keratoses, melasma, lentigines, age spots, liver spots, pigmented spots, wrinkles, blemishes, skin lines, oily skin, acne, warts, exzema, purutic skin, psoriasis, inflammatory dermatoses, distubted keratinization, skin changes associated with aging, nail or skin requiring cleansers, conditioning or treatment, and hair requiring conditioning or shampooing.

28. A composition comprising a cylic ester of hydroxyacids, present in a therapeutically effective amount in a pharmaceutically acceptable vehicle for topical treatment of cosmetic conditions and dermatologic disorders wherein,

said cylic ester of hydroxyacids is at least one member having the following structure:



wherein Ra and Rb are H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain, having 1 to 25 carbon atoms, or cyclic form having 5 or 6 ring members, and n is 2 or any number up to 200; Ra and Rb in monomer unit 2 through 200 may be the same or the different groups from that in monomer unit 1; the hydrogen atom in Ra and Rb may be substituted by a halogen atom-or a radical of lower alkyl, aralkyl, aryl or alkoxy of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain, having 1 to 9 carbon atoms, or cyclic form having 5 to 6 ring members, and the acyclic esters of hydroxyacids being present as a free acid, ester or in a salt form with an organic base or inorganic alkali in a pharmaceutically acceptable vehicle.

29. The composition of claim 28, wherein said cyclic ester of hydroxyacids is selected from the group consisting of glycolide, lactide, mandelide, atrolactide, phenyllactide, benzilide, methyllactide, lactoglycolide and glycolactide.

30. The composition of any one of claims 28 and 29, further comprising a cosmetic agent or a pharmaceutical agent for topical treatment of dermatological disorders.

31. The composition of claim 30, wherein the cosmetic agent or pharmaceutical agent is selected from the group consisting of cosmetic or pharmaceutical agent is selected from the group consisting of clotrimazole, ketoconazole, miconazole, griseofulvin, hydroxyzine, diphenhydramine, pramoxine, lidocaine, procaine, mepivacaine, hydroquinone,  
5 monobenzene, erythromycin, tetracycline, clindamycin, meclocycline, minocycline, naproxen, ibuprofen, theophylline, cromolyn, albuterol, retinoic acid, 13-cis retinoic acid, hydrocortisone, hydrocortisone 21-acetate, hydrocortisone 17-valerate, hydrocortisone 17-butyrate, betamethasone dipropionate, triamcinolone acetonide, fluocinonide, clobetasol propionate, benzoyl peroxide, crotamiton, propranolol, promethazine, vitamin A palmitate  
10 and vitamin E acetate.

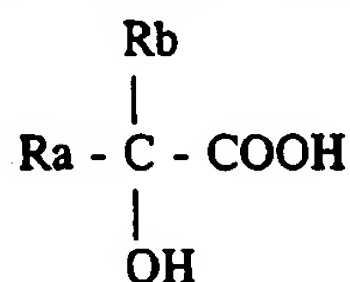
32. The composition of claim 30, wherein said cosmetic or pharmaceutical agent is selected from the group consisting of agents that improve or eradicate age spots, keratoses and wrinkles; analgesics; anesthetics; antiacne agents; antibacterials; antiyeast agents; antifungal agents; antiviral agents; antidandruff agents; antidermatitis agents; antipruritic  
5 agents; antiemetics; antimotionsickness agents; antiinflammatory agents; antihyperkeratolytic agents; antidry skin agents; antiperspirants; antipsoriatic agents; antiseborrheic agents; hair conditioners and hair treatment agents; antiaging and antiwrinkle agents; antiasthmatic agents and bronchodilators; sunscreen agents; antihistamine agents; skin lightening agents; depigmenting agents; vitamins; corticosteroids; tanning agents; hormones; retinoids; topical  
10 cardiovascular agents or dermatologicals.

33. The composition of claim 28, wherein said cosmetic conditions and dermatologic disorders are selected from the group consisting of dry skin, xerosis, ichthyosis, dandruff, brownish spots, keratoses, melasma, lentigines, age spots, liver spots, pigmented spots, wrinkles, blemishes, skin lines, oily skin, acne, warts, exzema, puritic skin, psoriasis,

- 5 inflammatory dermatoses, disturbed keratinization, skin changes associated with aging, nail or skin requiring cleansers, conditioning or treatment, and hair requiring conditioning or shampooing.

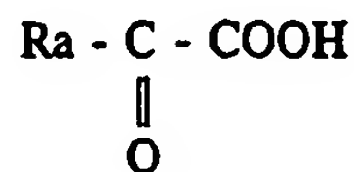
34. A method of alleviating aging related skin changes comprising topically applying to a subject in need thereof, a therapeutically effective amount of at least an alpha hydroxyacid, an alpha ketoacid or a related compound, for a period of time sufficient to alleviate said aging related skin change,

- 5 said alpha hydroxyacid being at least one member selected from the group consisting of alkyl alpha hydroxyacid, aralkyl and aryl alpha hydroxyacid, polyhydroxy alpha hydroxyacid and polycarboxylic alpha hydroxyacid having the following chemical structure:



- 10 wherein Ra and Rb are H, F, Cl, Br, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-someric, straight or branched chain, having 1 to 25 carbon atoms, or cyclic form having 5 or 6 ring members, and in addition Ra and Rb may carry OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms, said alpha hydroxyacid existing as a free acid or lactone form, or in salt form with an organic base or an inorganic alkali, and as stereoisomers as D, L, and DL forms when Ra and Rb are not identical;

- 15 said alpha ketoacid being at least one member selected from a group of compounds represented by the following chemical structure:



wherein Ra is H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain, having 1 to 25 carbon atoms, or cyclic form having 5 or 6 ring members, and in addition Ra may carry F, Cl, Br, I, OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms, said alpha ketoacid existing as a free acid or in a salt form with an organic base or an inorganic alkali; and

said related compound being at least one member selected from the group consisting of ascorbic acid, quinic acid, isocitric acid, tropic acid, trethocanic acid, 3-chlorolactic acid, cerebronic acid, citramalic acid, agaricic acid, 2-hydroxynervonic acid, aleuritic acid and pantoic acid, with the proviso that 2-hydroxyoctanoic acid and 2-ketooctanoic acid are excluded.

35. The method of claim 34, wherein said alkyl alpha hydroxyacid is at least one member selected from the group consisting of 2-hydroxyethanoic acid (glycolic acid), 2-hydroxypropanoic acid (lactic acid), 2-methyl 2-hydroxypropanoic acid (methyl lactic acid), 2-hydroxybutanoic acid, 2-hydroxypentanoic acid, 2-hydroxyhexanoic acid, 2-hydroxyheptanoic acid, 2-hydroxynonanoic acid, 2-hydroxydecanoic acid, 2-hydroxyundecanoic acid, 2-hydroxydodecanoic acid (alpha hydroxylauric acid), 2-hydroxytetradecanoic acid (alpha hydroxymyristic acid), 2-hydroxyhexadecanoic acid (alpha hydroxypalmitic acid), 2-hydroxyoctadecanoic acid (alpha hydroxystearic acid) and 2-hydroxyeicosanoic acid (alpha hydroxyarachidonic acid).

36. The method of claim 34, wherein said aralkyl and aryl alpha hydroxyacid is selected from the group consisting of 2-phenyl 2-hydroxyethanoic acid (mandelic acid), 2,2-diphenyl 2-hydroxyethanoic acid (benziliacid), 3-phenyl 2-hydroxypropanoic acid (phenyllactic acid), 2-phenyl 2-methyl 2-hydroxyethanoic acid (atrolactic acid), 2-(4'-hydroxyphenyl) 2-hydroxyethanoic acid, 2-(4'-chlorophenyl) 2-hydroxyethanoic acid, 2-(3'-hydroxy-4'-methoxyphenyl) 2-hydroxyethanoic acid, 2-(4'-hydroxy-3'-methoxyphenyl) 2-hydroxyethanoic acid, 3-(2'-hydroxyphenyl) 2-hydroxypropanoic acid, 3-(4'-hydroxyphenyl) 2-hydroxypropanoic acid and 2-(3',4'-dihydroxyphenyl) 2-hydroxyethanoic acid.



37. The method of claim 34, wherein said polyhydroxy alpha hydroxyacid and polycarboxylic alpha hydroxyacid is at least one member selected from the group consisting of 2,3-Dihydroxypropanoic acid (Glyceric acid), 2,3,4-Trihydroxybutanoic acid and Isomers erythronic acid and threonic acid, 2,3,4,5-Tetrahydroxypentanoic acid and Isomers ribonic acid, arabinoic acid, xylonic acid and lyxonic acid, 2,3,4,5,6-Pentahydroxyhexanoic acid and Isomers allonic acid, altronic acid, gluconic acid, mannoic acid, gulonic acid, idonic acid, galactonic acid and talonic acid, 2,3,4,5,6,7 Hexahydroxyheptanoic acid and Isomers glucoheptonic acid and galactoheptonic acid, 2-Hydroxypropane-1,3-dioic acid (Tartronic acid), 2-Hydroxybutane-1,4-dioic acid (Malic acid), 2,3-Dihydroxybutane-1,4-dioic acid (Tartaric acid), 2-Hydroxy-2-carboxypentane-1,5-dioic acid (citric acid), 2,3,4,5-Tetrahydroxyhexane-1,6-dioic acid and Isomers saccharic acid and mucic acid, or lactone forms gluconolactone, galactonolactone, galactonolactone, glucuronolactone, galacturonolactone, gulonolactone, ribonolactone, saccharic acid lactone, pantoyllactone, glucoheptonolactone, mannonolactone and galactoheptonolactone.

38. The method of claim 34, wherein said alpha ketoacid is at least one member selected from the group consisting of 2-Ketoethanoic acid (Glyoxylic acid), 2-Ketopropanoic acid (Pyruvic acid), 2-Phenyl-2-ketoethanoic acid (Benzoylformic acid), 3-Phenyl-2-ketopropanoic acid (Phenylpyruvic acid), 2-Ketobutanoic acid, 2-Ketopentanoic acid, 2-Ketohexanoic acid, 2-Ketoheptanoic acid, and 2-Ketododecanoic acid.

39. The method of claim 34, wherein said composition further comprises a cosmetic agent or a pharmaceutical agent.

40. The method of claim 39, wherein the cosmetic agent or pharmaceutical agent is selected from the group consisting of cosmetic or pharmaceutical agent is selected from the group consisting of clotrimazole, ketoconazole, miconazole, griseofulvin, hydroxyzine, diphenhydramine, pramoxine, lidocaine, procaine, mepivacaine, hydroquinone, monobenzene, erythromycin, tetracycline, clindamycin, meclocycline, minocycline,



naproxen, ibuprofen, theophylline, cromolyn, albuterol, retinoic acid, 13-cis retinoic acid, hydrocortisone, hydrocortisone 21-acetate, hydrocortisone 17-valerate, hydrocortisone 17-butyrate, betamethasone dipropionate, triamcinolone acetonide, fluocinonide, clobetasol propionate, benzoyl peroxide, crotamiton, propranolol, promethazine, vitamin A palmitate  
10 and vitamin E acetate.

41. The method of claim 39, wherein said cosmetic or pharmaceutical agent is selected from the group consisting of agents that improve or eradicate age spots, keratoses and wrinkles; analgesics; anesthetics; antiacne agents; antibacterials; antiyeast agents; antifungal agents; antiviral agents; antidandruff agents; antidermatitis agents; antipruritic  
5 agents; antiemetics; antimotionsickness agents; antiinflammatory agents; antihyperkeratolytic agents; antidry skin agents; antiperspirants; antipsoriatic agents; antiseborrheic agents; hair conditioners and hair treatment agents; antiaging and antiwrinkle agents; antiasthmatic agents and bronchodilators; sunscreen agents; antihistamine agents; skin lightening agents; depigmenting agents; vitamins; corticosteroids; tanning agents; hormones; retinoids; topical  
10 cardiovascular agents or dermatologicals.

42. The method of claim 34, wherein said aging related skin changes are selected from the group consisting of: diminution in the number of elastic fibers in the papillary dermis; diminution in the diameter of elastic fibers in the papillary dermis; sun damage; excessive deposition of abnormal elastic materials in the upper dermis; thickening of the  
5 skin; atrophy of the dermis; reduction in subcutaneous adipose tissue; yellowing of the skin; loss of collagen in the dermis; and reduction of glycosaminoglycans in the dermis.

43. A composition as claimed in claim 1, 10 or 28, substantially as herein described with reference to any one of the Examples.

44. A method as claimed in claim 34, substantially as herein described with reference to any one of the Examples.

DATED this 25th Day of June 1998

RUEY J. YU and EUGENE Y. VAN SCOTT

DATED this Attorney: RUTH M. CLARKSON  
Fellow Institute of Patent Attorneys of Australia  
of SHELSTON WATERS

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## ABSTRACT

The invention relates to a composition comprising a complex formed from the reaction of an amphoteric or pseudoamphoteric agent and at least one compound selected  
5 from the group consisting of an alpha hydroxyacid, an alpha ketoacid or a related compound. The invention also relates to the use of these compositions in the topical treatment of cosmetic conditions or dermatologic disorders.

